A Phase 1/2, Placebo-Controlled, Randomized Study to Evaluate the Safety, Immune Response and Clinical Activity of HS-410 in Patients with Non-Muscle Invasive Bladder Cancer Who Have Undergone Transurethral Resection of Bladder Tumor (TURBT)

Protocol HS410-101

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Date	Version	Amendment Number	Amendment Type
25 Sep 2013	1.0	Initial Protocol	Not applicable
5 Nov 2013	2.0	1	Non-substantial
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Sponsor:
Melissa Price, PhD
Heat Biologics, Inc.
801 Capitola Drive, Suite 12
Durham, NC 27713
Tel: 919-240-7133

Medical Monitor:
Pia Lynch, M.D.
Drug Safety Solutions
5205 Indigo Moon Way
Raleigh, NC 27613
Tel: 770-826-1096
Fax: 678-828-5549

Primary Investigator:
Gary D. Steinberg, M.D.
The Bruce and Beth White Family Professor and Director of Urologic Oncology
Vice Chairman Section of Urology
University of Chicago Medical Center
5841 S. Maryland Avenue, MC 6038
Chicago, Illinois 60637
Tel: 773-702-3080
Fax: 773-702-1001

SPONSOR PROTOCOL APPROVAL PAGE

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Amendment #: 7

Version #: 8.0

Version Date: 03-Feb-2016

I, the undersigned, have read this protocol and confirm that to the best of my knowledge it accurately described the planned conduct of the study. I hereby approve this protocol for release to clinical trial sites.

Mel Price

3-Feb-2016

Melissa Price, PhD
Vice President, Clinical and Regulatory Affairs
Heat Biologics

Approval Date

INVESTIGATOR PROTOCOL AGREEMENT PAGE

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Version/Date: Version 8.0 (03 Feb 2016)

I understand that all documentation provided to me by Heat Biologics, Inc., or its designated representative(s) concerning this study that has not been published previously will be kept in the strictest confidence. This documentation includes the study protocol, investigator's brochure, case report forms, and other scientific data.

This study will not commence without the prior written approval of a properly constituted Institutional Review Board (IRB) and Institutional BioSafety Committee (IBC), as applicable. No changes will be made to the study protocol without the prior written approval of Heat Biologics, Inc., and the IRB and/or IBC, except where necessary to eliminate an immediate hazard to the patient.

I have read and understand the clinical protocol and agree to conduct the clinical study in compliance with the protocol, Good Clinical Practice, the Declaration of Helsinki (2008), United States and other applicable local regulatory requirements.

Principal Investigator Name, printed: _____

Principal Investigator Signature:_____

Date: _____

CLINICAL PROTOCOL SYNOPSIS

Trial title:	A Phase 1/2, Placebo-Controlled, Randomized Study to Evaluate the Safety, Immune Response and Clinical Activity of HS-410 in Patients with Non-Muscle Invasive Bladder Cancer Who Have Undergone Transurethral Resection of Bladder Tumor (TURBT)
Study objectives:	Primary Objective: • **Phase 1:** To characterize the safety and tolerability of low dose monotherapy vaccination with vesigenurtacel-L in patients with non-muscle invasive bladder cancer. • **Phase 2:** o Arms 1, 2, and 3: To evaluate 1-year disease-free survival in patients with non-muscle invasive bladder cancer treated with BCG in combination with blinded study product (one of two doses of vesigenurtacel-L or placebo). o Arm 4: To evaluate 1-year disease-free survival in patients with non-muscle invasive bladder cancer treated with high dose vesigenurtacel-L monotherapy. Secondary Objectives: • To evaluate the safety of the combination of vesigenurtacel-L and BCG (Phase 2 only) • To evaluate the safety of high dose vesigenurtacel-L monotherapy (Phase 2 only) • To evaluate the proportion of patients with recurrence at 3, 6, 12, 18, and 24 months • To evaluate the proportion of patients with progressive disease at 3, 6, 12, 18, and 24 months • To evaluate disease-free survival at 3, 6, 18 and 24 months • To evaluate overall disease-free survival • To evaluate overall survival (OS) • To evaluate the proportion of patients undergoing post-treatment TURBT or fulguration by 12 and 24 months • To evaluate the proportion of patients undergoing cystectomy by 12 and 24 months • To evaluate the proportion of patients with immunologic response of PBMCs via intracellular cytokine staining (ICS) by flow cytometry and/or ELISPOT on CD8+ cells following vesigenurtacel-L vaccination Exploratory Objectives: • Immunologic response of PBMCs (analysis of surface markers, CD3, CD4, CD8, CD19, CD25, CD45, CD56, FoxP3, and degranulation) and stimulation analysis via ICS of IFNγ and granzyme B (gzB). • Total PBMC counts by flow cytometry, including lymphocyte subsets (B cells, helper T-cells, cytotoxic T-cells, NK cells and T-reg) • Evaluation of tumor tissue obtained prior to treatment for antigen expression, expression of major histocompatibility complex (MHC) class I, and expression of immunosuppressive molecules • Evaluation of tumor tissue obtained from repeat biopsy, if clinically indicated, for presence of tumor infiltrating T-lymphocytes (TILs) • T cell receptor sequencing of PBMCs and tumor tissue to determine correlation between clonally expanded T cell populations and other endpoints • Immune cell infiltration and inflammatory cytokine levels in urine (Phase 2 only)
Trial centers:	Up to 20 centers

Sample size:	Approximately 110 patients will be enrolled in the study in order to obtain 10 patients in Phase 1 and 100 patients in Phase 2.
Trial design:	Patients with non-muscle invasive bladder cancer who have either undergone TURBT or fulguration for the removal of papillary disease or who have carcinoma in situ (CIS) only, are candidates for BCG treatment, and are judged to be at an increased risk for recurrence are eligible if they are BCG naive or have completed previous BCG treatment >12 months prior to the baseline staging procedure. Phase 2 also allows patients who will not otherwise receive BCG. The Phase 1 portion is an open-label, safety study consisting of one cohort with 10 patients. Patients will have previously received 3-6 instillations of weekly intravesical BCG induction therapy (as standard of care) followed by low dose intradermal (1×10^6 cells) vesigenurtacel-L (HS-410) monotherapy. In Phase 2, patients will be assigned to treatment groups based on whether they will receive induction BCG in the typical post-TURBT window. If the investigator plans to administer BCG, patients will be randomized to one of three blinded (physician-patient), placebo-controlled groups and receive either intradermal placebo or low dose or high dose (1×10^7 cells) vesigenurtacel-L in combination with induction and maintenance intravesical BCG. If patients will not receive BCG, they will be enrolled into an open-label, non-randomized group and receive high dose intradermal vesigenurtacel-L monotherapy. Phase 1: Patients enrolled in the first cohort within 8-10 weeks of TURBT or fulguration for patients with papillary disease and staging procedure for patients with CIS only, and after induction BCG will be treated with vesigenurtacel-L weekly for 6 weeks. After a one-week vaccine holiday for disease assessment, patients will receive vesigenurtacel-L for an additional 6 weeks followed by three once monthly treatments for a total of 15 vaccinations. Patients will be observed weekly to assess the safety of vesigenurtacel-L. Dosing of the first three patients will be staggered by two-week intervals to allow for safety evaluation before treating additional patients. If vesigenurtacel-L appears safe and well-tolerated in the 3 lead-in patients, dosing will be continued to 10 patients. Phase 2: Dosing in Phase 2 will begin when all 10 patients have been dosed in the Phase 1 cohort, at least 6 patients in that cohort have completed the Week 7 safety assessments, and the Data Monitoring Committee (DMC) has met to review this data and agreed it is safe to advance to Phase 2. A total of 100 patients will be assigned to four groups: 75 who will receive BCG will be randomized to arms combining either low dose vesigenurtacel-L, high dose vesigenurtacel-L, or placebo, respectively, with induction and maintenance BCG; 25 who will not receive BCG will be enrolled in the high dose vesigenurtacel-L monotherapy arm. In the randomized arms, treatment will commence within 6 weeks of the most-recent TURBT or fulguration for patients with papillary disease and staging procedure for patients with CIS only. Patients will be treated during an induction phase with weekly intravesical BCG and intradermal blinded study product (vesigenurtacel-L or placebo) for 6 weeks followed by 6 weekly injections of blinded study product alone. During a subsequent maintenance phase, patients will receive an additional three courses of three once-weekly blinded study product injections in combination with intravesical BCG approximately 3, 6, and 12 months after initiating induction BCG. Patients may receive additional courses of maintenance BCG in long-term follow-up at the investigator's discretion but should not receive any other cancer therapy prior to disease recurrence/progression.

Trial design (con't):	In the monotherapy arm, treatment will commence within 6 weeks of the most-recent TURBT or fulguration for patients with papillary disease and staging procedure for patients with CIS only. Patients will be treated during an induction phase with weekly intradermal vesigenurtacel-L for 12 weeks. During a subsequent maintenance phase, patients will receive an additional three courses of three once-weekly vesigenurtacel-L injections approximately 3, 6, and 12 months after initiating induction vesigenurtacel-L. All patients in both the Phase 1 and Phase 2 portions of the study will have a cystoscopy and cytology and, if clinically indicated, a biopsy performed approximately every 3 months for 2 years then every 6 months for up to a year, study termination, disease progression, or recurrence requiring treatment discontinuation, whichever occurs first. Patients with evidence of disease at an assessment may continue on treatment if judged by the investigator to be in the patient's best interest (e.g. would normally receive another course of BCG therapy as standard of care (SOC)). Upon discontinuation of study treatment, additional treatment will be at the discretion of the treating physician per SOC. While treatment may continue in the presence of evidence of disease, statistical analysis of disease-free status will still follow strict definitions as defined in section 10.1. Evaluation of Disease.
Dosing regimen:	**Phase 1**: Patients will receive weekly intradermal injections of low dose vesigenurtacel-L (1×10^6 cells per dose) for 12 weeks with a vaccine holiday on Week 7 to allow for assessment of evidence of disease, followed by three once-monthly injections for a total of 15 doses. **Phase 2**: In the randomized arms, patients will receive weekly intradermal injections of blinded study drug product (one of two doses of vesigenurtacel-L or placebo) in combination with intravesical induction BCG for 6 weeks followed by 6 weeks of blinded study product monotherapy with a vaccine holiday on Week 13 to allow for assessment of evidence of disease, followed by three courses of three once-weekly injections of blinded study product in combination with maintenance BCG for a total of 21 doses. **Vesigenurtacel-L:** Arm 1: Vesigenurtacel-L consisting of 1×10^6 cells per dose Arm 2: Vesigenurtacel-L consisting of 1×10^7 cells per dose Arm 3: Placebo **BCG:** A full dose according to the investigator's standard practice should be administered. In the monotherapy arm (Arm 4), patients will receive weekly intradermal injections of high dose (1×10^7 cells per dose) vesigenurtacel-L for 12 weeks, followed by three courses of three once-weekly vesigenurtacel-L injections for a total of 21 doses.

Dosage form and route	Each study product dose will be divided into the number of injections required to reach the number of cells per dose with no more than 0.1 mL per injection (approximately 4-6 injections), and administered as spatially divided intradermal injections in the same extremity to increase volume distribution and enhance antigen presentation to lymph node regions shared with the urinary bladder. Dosing will rotate injection site extremities every four timepoints: antero-lateral left thigh, antero-lateral right thigh, left buttock, and right buttock. If injection site reactions are reported as an AE, an alternative injection site may be used upon discussion with the sponsor. **Vesigenurtacel-L:** Derived from irradiated urothelial bladder cancer cells expressing HLA-A1 on at least 70% of the cells, producing ≥ 60 ng of gp96-Ig/24h per 1 x 10^6 cells with ≥ 70% viability by trypan blue exclusion. Vesigenurtacel-L is provided as single-dose vials either 1) as concentrated frozen liquid, which will require dilution by the pharmacy with sterile saline, or 2) as fully-diluted frozen liquid not requiring additional dilution. In either case the final drug product will consist of cells resuspended in buffered saline containing human serum albumin (HSA), dimethyl sulfoxide (DMSO), and pentastarch and will be delivered at doses of either 1 x 10^6 cells or 1 x 10^7 cells. **Placebo:** 0.15% Intralipid solution in freezing solution (buffered saline, HSA, DMSO and pentastarch) without vesigenurtacel-L cells. **BCG:** Intravesical administration according to the institution's practice

Eligibility criteria:	**Inclusion Criteria:** 1. Willing and able to sign informed consent and comply with the protocol, including clinic visits to receive weekly vesigenurtacel-L injections for 12 doses followed by either monthly vesigenurtacel-L injections for three months in Phase 1 or three courses of three once-weekly injections in Phase 2. 2. Histologically or cytologically confirmed non-muscle invasive bladder cancer [Ta, T1 or Tis (CIS)]. Papillary disease must have been removed by transurethral resection or fulguration. 3. Either i. High-risk disease, defined as T1 and/or high-grade and/or CIS, *or* ii. Intermediate-risk disease defined as Ta low-grade with at least three of the following four risk factors: multiple tumors, tumor size > 3cm, early recurrence (<1 year from previous staging procedure), or recurrence with a frequency of more than once in any 12 month period 4. Patients must be BCG naïve or have completed previous BCG treatment >12 months prior to the baseline staging procedure. 5. For Phase 2 only: Arms 1, 2, and 3: Suitable, in the opinion of the investigator, to receive a 6-week course of induction intravesical BCG in the adjuvant setting within 6 weeks following the baseline staging procedure for the current occurrence of non-muscle invasive bladder cancer. Arm 4: Suitable for monotherapy vaccine administration post-TURBT. For Phase 1 only: Has previously received 3-6 weekly doses of BCG. 6. Age ≥18 years 7. Lab parameters: o Albumin ≥2.5 mg/dL o Total bilirubin <1.5 mg/dL o Alanine transaminase (ALT) and aspartate transaminase (AST) ≤2.5 × upper limit of normal (ULN) o Serum creatinine ≤2.2mg/dL or calculated creatinine clearance >35 mL/minute per the Cockcroft-Gault formula o White blood cell (WBC) count ≥4,000/mm^3 with an absolute neutrophil count ≥1,500/mm^3 o Hemoglobin ≥9 g/dL o Platelet count ≥75,000/mm^3 8. Women of childbearing potential or men of fathering potential must use adequate birth control measures (e.g., abstinence, oral contraceptives, intrauterine device, barrier method with spermicide, or surgical sterilization) during the study and for 6 months after receiving the last administration of study medication. Female patients of childbearing potential must test negative for pregnancy prior to enrolling in the trial.

Eligibility criteria (con't):	**Exclusion Criteria:** 1. Known human immunodeficiency virus (HIV) infection or immunodeficiency disorders, either primary or acquired 2. Infections or concurrent illness, requiring active therapy 3. Any condition requiring active steroid or other immunosuppressive therapy 4. Active malignancies within 12 months with the exception of those with a negligible risk of metastasis or death treated with expected curative outcome 5. Prior prostatic pelvic radiation within the past 12 months 6. Known history of clinically significant cardiac impairment, congestive heart failure > New York Heart Association (NYHA) cardiac disease classification Class II, unstable angina, or myocardial infarction during the previous three months 7. Known current alcohol or chemical abuse, or mental or psychiatric condition precluding compliance with the protocol 8. Pregnant or nursing 9. Known allergy to soy, egg, or peanut products 10. Receiving another investigational agent (30 day wash-out required prior to first dose) 11. Neo-adjuvant therapy prior to the baseline staging procedure for the current occurrence of non-muscle invasive bladder cancer 12. Prior treatment with a cancer vaccine for this indication 13. Prior vaccination with BCG for tuberculosis disease 14. Prior splenectomy
Safety monitoring:	All patients will be assessed for pre-existing symptoms during screening (from the date of signature of informed consent to immediately prior to first dose of study product). Symptoms will be documented as AEs only if related to study procedures from the first dose of study product until four weeks after the last dose of study product or until death, whichever occurs first. All AEs will be followed until the event has subsided or, in the case of permanent impairment, until the condition stabilizes. All patients who receive at least one dose of study product will be included in the safety analysis. The Primary Investigator and the Medical Monitor will assess the safety of vesigenurtacel-L on an ongoing basis during trial enrollment and dosing. A Data Monitoring Committee (DMC) will provide dose expansion recommendations during Phase 1 and will continue safety surveillance in Phase 2. In order to continually monitor safety during the Phase 2 portion, the DMC will review (unblinded) all available safety data after at least one patient has been randomized to each of the active arms and has completed four weeks of treatment and then after 3, 6, and 12 patients in each randomized treatment group have completed the Week 7 assessment. Subsequently the DMC will review all available safety data at regular three-monthly intervals until study completion or should they determine that review is no longer necessary. Additionally, the DMC will convene on an ad-hoc basis should any patient experience a Grade 3 or higher adverse event (considered by the investigator to be related to vesigenurtacel-L) at any time during the study. Depending on emerging data, the DMC will have the authority to suspend allocation to a particular study treatment and require that additional patients are studied in a particular arm or at a particular dose level of vesigenurtacel-L, in order to further characterize the safety profile.

Efficacy parameters:	Primary Endpoints: Phase 1: Safety and tolerability Phase 2: 1-year Disease-Free Survival (1-yr DFS) Secondary Endpoints: • Safety of the combination of vesigenurtacel-L and BCG (Phase 2 only) • Safety of high dose vesigenurtacel-L monotherapy (Phase 2 only) • Proportion of patients with recurrence at 3, 6, 12, 18, and 24 months • Proportion of patients with progressive disease at 3, 6, 12, 18, and 24 months • Disease-free survival (DFS) at 3, 6, 18, and 24 months • Overall DFS • Overall Survival (OS) • Proportion of patients undergoing post-treatment TURBT or fulguration by 12 and 24 months • Proportion of patients undergoing cystectomy by 12 and 24 months • Proportion of patients with immunologic response of PBMCs via intracellular cytokine staining (ICS) by flow cytometry and/or ELISPOT on CD8+ cells after receiving vesigenurtacel-L treatment as compared to baseline Exploratory Endpoints: • Immunologic response of PBMCs (analysis of surface markers, CD3, CD4, CD8, CD19, CD25, CD45, CD56, FoxP3, and degranulation) and stimulation analysis via ICS of IFNγ and gzB • Total PBMC counts by flow cytometry, including lymphocyte subsets (B cells, helper T-cells, cytotoxic T-cells, NK cells and T-reg) • Evaluation of tumor tissue obtained prior to treatment for antigen expression, expression of major histocompatibility complex (MHC) class I, and expression of immunosuppressive molecules by mRNA expression and/or immunohistochemical analysis • Evaluation of tumor tissue obtained from repeat biopsy, if clinically indicated, for presence of infiltrating T-lymphocytes (TILs) • T cell receptor sequencing of PBMCs and tumor tissue to determine correlation between clonally expanded T cell populations and other endpoints • Immune cell infiltration and inflammatory cytokine levels in urine (Phase 2 only)

Statistical methods:	Patients will be randomized centrally using a stratified block design according to risk of recurrence (strata: high vs. intermediate risk) and CIS (strata: yes vs. no) for Arms 1-3. Patients who will not receive BCG will be consecutively allocated into a fourth arm consisting of vaccine monotherapy. Efficacy comparisons between the monotherapy arm and any of the randomized arms will remain exploratory. However, safety and point estimates with appropriate measures of variance (SD, 95% CI) for the efficacy parameters will be estimated. For the randomized portion, the sample size is based on the hypothesis that the addition of vesigenurtacel-L to BCG versus BCG alone will improve disease-free survival at one year. The sample size will be 75 patients randomized into two experimental groups consisting of BCG plus low dose vesigenurtacel-L (1×10^6 cells per dose) and BCG plus high dose vesigenurtacel-L (1×10^7 cells per dose) and to a control group consisting of BCG plus placebo (final allocation = 25 vs 25 vs. 25) to provide 46 events in the experimental groups and 23 events in the control group. By assuming an alpha of 10% (one tailed), the randomized portion should have an 80% power to detect a 30% reduction in the risk of disease recurrence, progression, or death (control = 60% disease-free and alive vs. 90% in vesigenurtacel-L groups) at one year. There will be no adjustment for multiplicity in the comparison of the primary endpoint between the experimental groups and the control. The primary endpoint (proportion of patients alive and disease-free at one year) between the two experimental groups and the control will be compared using Fisher's exact test and presented as odds ratios (OR) with 95% confidence intervals (CI) relative to the control group. ORs will be generated via a simple logistic regression model with one year disease-free survival as the dependent variable and group as the sole independent variable (low dose and high dose vesigenurtacel-L vs. control). If the analysis of the primary endpoint does not suggest any dose response effect between the two vaccine arms, an exploratory analysis will be conducted where the two vaccine arms will be pooled and compared to the control arm for the primary endpoint (proportion of patients alive and disease-free at one year). The outcome will be presented as OR with 95% CI relative to the control group. Binary secondary endpoints will be presented as ORs with appropriate 95% CI. For the time to event endpoints (i.e. overall DFS and OS), survival curves will be generated by the method of Kaplan-Meier and compared with the log-rank test. In an exploratory analysis, the weighted log rank test will also be used. The weighted log rank preserves the statistical power that is lost due to the lag time effect in efficacy with immunotherapeutic agents. In a supporting analysis, a simple Cox proportional hazards model with treatment group as the sole independent variable will be built in order to estimate the hazard rate (HR) and 95% CI for DFS between the low and high dose vesigenurtacel-L groups relative to the control. In an exploratory analysis, patients experiencing an immune response in all four treatment arms will be compared to those who did not experience an immune response. The analysis will include a univariate comparison of patient and clinical variables at baseline

Statistical methods (con't):	as well as a comparison of any difference between immune responders and non-responders for the following endpoints: proportion with progressive or recurrent disease at selected time points, disease-free survival, proportion undergoing post-treatment TURBT or fulguration or cystectomy and overall survival. In an additional exploratory analysis, the proportion of patients whose disease has recurred to a lower stage than at screening and the proportion of patients whose disease has recurred to the same extent as at screening will be compared between the experimental and control groups at the 6, 12, 18, and 24 month time points and presented as an OR with 95% CI.

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LIST OF ABBREVIATIONS

AE	Adverse event
AJCC	American Joint Committee on Cancer
ALT	Alanine transaminase
AST	Aspartate transaminase
AT	As treated
BCG	Bacillus Calmette–Guérin
cGMP	current Good Manufacturing Practices
CIS	Carcinoma in situ
CTCAE	Common toxicity criteria for adverse events
DMC	Data Monitoring Committee
DMSO	Dimethyl sulfoxide
ECG	Electrocardiogram
ECRF	Electronic case report form
ELISA	Enzyme-linked immunosorbent assay
EX	Excluded subject
EOT	End of treatment
ESR	Erythrocyte sedimentation rate
FACS	Fluorescent-activated cell sorter
FFPE	Formalin-fixed, paraffin-embedded
FDA	Food and Drug Administration
GCP	Good Clinical Practice
gzB	Granzyme B
HIV	Human immunodeficiency virus
IEC	Independent ethics committee
IHC	Immunohistochemistry
IBC	Institutional biosafety committee
IBCG	International Bladder Cancer Group
ICS	Intracellular cytokine staining
IFNγ	Interferon gamma
IHC	Immunohistochemistry
IND	Investigational New Drug (application)
IRB	Institutional Review Board
ISR	Injection site reaction
ITT	Intent to treat (population)
MedDRA	Medical dictionary for regulatory activities
MHC	Major histocompatibility complex
NCI	National Cancer Institute
NED	No evidence of disease
NMIBC	Non-muscle invasive bladder cancer
NSCLC	Non-small cell lung cancer
NYHA	New York Heart Association
OS	Overall survival
PBMC	Peripheral blood mononuclear cell

PCR	Polymerase chain reaction
PFS	Progression free survival
POC	Proof of concept
PP	Per Protocol
PT	Preferred term
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAR	Suspected adverse reaction
SD	Standard deviation
SOE	Schedule of events
SOC	Standard of care
TCR	T-cell receptor
TURBT	Transurethral resection of bladder tumor
ULN	Upper limits of normal
WBC	White blood cell

1.0 BACKGROUND

1.1 Bladder Cancer

Bladder cancer is the 6th most common cancer in the United States with an estimated 74,690 patients diagnosed in 2014 and 15,580 deaths. [1,2] Worldwide, 2.7 million people are living with a history of bladder cancer.[2] Bladder cancer is estimated to be the most costly cancer in the US, and treatment-related complications are estimated to account for one-third of total costs.[3,4]

Approximately 70-80% of patients have non-muscle invasive bladder cancer (NMIBC) at the time of diagnosis.[5,6] Transurethral resection of bladder tumor (TURBT) is the standard treatment for NMIBC and aids in the proper diagnosis and staging of disease.

Patients with low-risk disease (solitary, primary, low-grade, Ta tumors) have high recurrence-free and progression-free rates and an overall favorable prognosis.[6,7] In contrast, patients with high-risk disease (T1 and/or high grade and/or *carcinoma in situ (CIS)*) determined at the time of initial resection have a one year recurrence-free rate as low as 39%, and by five years, this rate has dropped even further to 20%.[6]

Between these two extremes is a large group of patients classified as having intermediate-risk disease, which is defined as multiple or recurrent, low-grade, Ta tumors.[7] Because this is a very broad spectrum of patients, the intermediate-risk category can be further stratified. Intermediate-risk patients with at least three of the following four risk factors – multiple tumors, tumor size > 3cm, early recurrence (<1 year from previous TURBT), or frequent recurrences (i.e. recurrence with a frequency of more than once in any 12-month period) – have treatment regimens and outcomes similar to high-risk patients, with recurrence-free rates of 62% at one year and 38% at five years.[6,8] Patients with either high-risk disease or intermediate-risk disease with three or more risk factors will make up the patient population for this protocol.

Adjuvant treatment options for patients with urinary bladder cancer are limited, as systemic chemotherapy appears largely ineffective in this setting.[9,10] Adjuvant intravesical mitomycin-C, often given as a single dose within 24 hours of surgery, and intravesical bacillus Calmette-Guérin (BCG), which cannot be initiated until several weeks after surgery to reduce the risk of sepsis, have been used successfully to reduce local recurrence of NMIBC for over 30 years, but nearly a quarter of high-risk patients have evidence of disease 6 months after induction BCG.[11] Patients with intermediate- or high-risk disease benefit most when induction BCG is combined with a maintenance phase lasting at least one year.[12,13,14,15] However, nearly 15% of these patients will still go on to experience a recurrence after three years.[15] Reasons for failure are not well defined but may be related to toxicities associated with these agents resulting in utilization of intravesical therapy well below recommended dose intensities.[16,17] More recently, access to BCG, itself, has become a significant treatment barrier due to production problems with manufacturers of the drug.

Because of the limited long term disease control possible with currently available adjuvant strategies in patients with high-risk NMIBC, the shortage of BCG, and the progressively less effective and more debilitating outcomes of subsequent rounds of surgical resection, there is a pressing need for alternate or complementary adjuvant strategies, such as vaccine-based immunotherapy, to reduce recurrence and improve tolerability of treatments in this patient group.

Immunologic surveillance is the mechanism by which cells undergoing malignant transformation are eliminated from the body through recognition by innate and adaptive immune cells. Immunotherapeutic

approaches designed to exogenously stimulate innate immune surveillance can be classified broadly under active immunotherapy/therapeutic vaccines, adoptive cellular immunotherapy, and passive immunotherapy.[18] Although most clinically advanced cancers have escaped immunological control mechanisms, the possibility that autologous cellular immunity can be restimulated to target cancer cells has led to a number of therapeutic trials of a variety of immunotherapy approaches.[19] These studies have demonstrated that improved overall survival can be achieved even in generally chemoresistant malignancies, such as advanced renal cancer, prostate cancer, and melanoma.[19,20,21,22] Immunomodulation is particularly appropriate in the context of minimal residual disease, such as immediately after TURBT, since it is believed that it may be the setting in which this approach is most effective.[23]

Recent advances in the immunotherapy field have led to the understanding that destruction of a tumor involves multiple coordinated immune mechanisms, including activation of antigen presenting cells and effector T cells, blockade of immune regulatory molecules, including CTLA-4 and PD-1, and reduction of suppressor T cells.[24] Additionally, it is now recognized that immunotherapeutic agents are frequently characterized by a period of latency between administration and subsequent clinical response, which is in contrast to traditional chemotherapeutic or small molecule regimens wherein the clinical response is predicted by and associated with the peak concentration of drug achieved shortly after administration. Furthermore, shortly after initiating immunotherapy treatment, patients may appear to experience disease progression as assessed by conventional imaging techniques, before the onset of biological activity and clinical effect.[25]

Greater understanding of the methodological complexity of assessing immunotherapeutic agents are now resulting in more appropriate clinical trial designs, which have significantly improved the probability of detecting the anti-cancer clinical utility of immunotherapeutic approaches in early stage clinical trials, such as the one described in this protocol.

1.2 Rationale for Vesigenurtacel-L Development

The hypotheses behind the development of vesigenurtacel-L (HS-410), a therapeutic vaccine, to treat urothelial cancer of the bladder are as follows:

(1) A range of tumor-associated antigens (survivin, LAGE-1, MAGE-A3, MAGE-A11, and PRAME) have been identified in bladder cancer, and it is postulated that treatment with BCG therapy provides the innate immune system with a warning signal to induce and direct an acquired immune response against such antigens.[26] However, BCG therapy is accompanied by a high failure rate and significant side effects, which limit its clinical application. The clinical response to BCG might be improved through concurrent enhancement of tumor immunogenicity by concomitant administration of a vaccine, such as vesigenurtacel-L, during standard BCG therapy.

(2) Secreted gp96-Ig from vesigenurtacel-L combines adjuvant activity with polyvalent peptide specificity. Vesigenurtacel-L activates dendritic cells (DC), natural killer (NK) cells, and cytotoxic T lymphocytes (CTL). Tumor cells can be killed by NK cell-specific mechanisms, by promiscuous killing by CD8+ CTL through NKG2D, and by major histocompatibility complex (MHC)-restricted CD8+ CTL activity. The activation of DC and NK cells by vesigenurtacel-L may also counteract the generation of immunosuppressive CD4+ regulatory cells.

(3) Vesigenurtacel-L also stimulates antigen cross presentation via the CD91 receptor, Toll-like receptor (TLR) 2 and TLR4 on DC and macrophages. Allogeneic tumor cells are likely to share public tumor antigens in analogy to melanoma. Therefore, allogeneic, gp96-secreting tumor cells used as a vaccine (such as vesigenurtacel-L) are expected to generate NK cell and CTL activity to the patient's autologous tumor.

(4) BCG activates innate immune receptors, primarily TLR, within the endothelial lining of the bladder following intravesical administration. Activation of these innate receptors contributes to the local production of inflammatory cytokines, including IL-1β and TNFα, which provide an inflammatory signal leading to upregulation of the local microvascular endothelium within the bladder wall, including expression of selectin ligands and integrins, such as ICAM-1 and VCAM-1.

Vesigenurtacel-L is administered intradermally and leads to the activation of antigen-specific CD8+ T cells that circulate through the systemic vasculature. Extravasation of T cells into tissues requires activation of endothelial cells, and trafficking through inflamed vessels is mediated by selectins, integrins, and chemokines. Thus, the systemic activation of T cells by vesigenurtacel-L is proposed to synergize with BCG through the combined increase in bladder-tumor antigen-specific T cells that may traffic more efficiently into the bladder due to endothelial activation by locally administered BCG.

Similarly, inflammation generated in response to the TURBT surgical procedure may drive CD8+ T cells into the bladder tissue, even in the absence of BCG, mediating CD8+ T cell trafficking to the bladder in a BCG-independent fashion. Initiating vaccination during the perioperative period immediately after TURBT potentially capitalizes on this period of post-operative immunoactivity.

(5) In current clinical practice, no treatment is typically administered during the 6 week period following completion of BCG induction therapy and prior to the next cystoscopy. Continued treatment with a vaccine, such as vesigenurtacel-L, during this time may provide an additional important window for continued immune stimulation, which could result in improved treatment response.

(6) Although it is postulated that concurrent administration of intravesical BCG and intradermal vesigenurtacel-L might result in optimally synergistic immunoactivation, it is also possible that intradermal vesigenurtacel-L monotherapy will result in a significant degree of immune modulation, independently of concomitant BCG. The current study will, therefore, examine vesigenurtacel monotherapy in patients who will not receive BCG.

1.3 Description of Investigational Agent Vesigenurtacel-L

Vesigenurtacel-L is a whole cell vaccine that has been irradiated to render cell replication incompetent while maintaining biological activity, i.e., expression of certain tumor-associated antigens as described above.

Vesigenurtacel-L is derived from a human prostate cancer cell line, PC3. This cell line was evaluated amongst others and was selected based on the overlap of its native antigenic profile with that of tumor

samples from patients with NMIBC. The chosen PC3 tumor cells were modified to express HLA-A1 protein and secrete gp96-Ig fusion protein by stable transfection. Clones with a high level of expression were obtained by G418 (Geneticin) selection and flow cytometry cell sorting.

Preparation of the drug product includes expansion of batches of cells using current good manufacturing practices (cGMP) manufacturing methods. The cells are tested for presence of expression of HLA-A1 by fluorescent-activated cell sorter (FACS) and gp96-Ig expression by enzyme-linked immunosorbent assay (ELISA). Cells are harvested, washed, resuspended in buffered saline, irradiated, washed and vialed. The vialed cells are frozen and then stored at ≤ -120°C in the vapor phase of a liquid nitrogen freezer.

1.4 Prior Human Experience

This is the first trial to dose patients with vesigenurtacel-L. A first-in-human Phase 1 study of HS-110, a lung cancer vaccine using the same technology platform, was conducted in 18 patients with advanced non-small cell lung cancer (NSCLC).[27] Patients received one of three dosing regimens. Safety was evaluated as a primary endpoint and tumor response and survival were secondary endpoints. Immune response in peripheral blood was characterized in 15 patients who received at least one course (6 weeks) of vaccination by measuring production of IFN-γ by patient CD8+ T cells as compared to baseline.

The majority of adverse events were mild injection site reactions, consisting mainly of rash, induration, pruritus, and pain. Six serious adverse events were reported for five patients: respiratory disorder for a patient who was enrolled but not treated with HS-110, disease progression (two patients), chest pain, and dyspnea and rectal hemorrhage. None of these events was considered by the investigator to be treatment-related.

None of the 18 patients had an objective tumor response by the Response Evaluation Criteria in Solid Tumors (RECIST). Fourteen patients had died, and four surviving patients were followed for a median of 10.6 months (range 2.6 to 16.6). The Kaplan-Meier estimate of median survival was 8.0 months (95% confidence interval [CI]: 6.7 to 18.2), and the 6, 12, and 24-month overall survival (OS) rates were 77.8% (95% CI: 51.1 to 91.0%), 41.9% (95% CI: 19.1 to 63.3%), and 11.2% (95% CI: 0.8 to 37.3%), respectively. All patients have now died.

2.0 OBJECTIVES

2.1 Primary Objective

Phase 1
To characterize the safety and tolerability of low dose monotherapy vaccination with vesigenurtacel-L in patients with non-muscle invasive bladder cancer

Phase 2
- Arms 1, 2, and 3: To evaluate 1-year disease-free survival in patients with non-muscle invasive bladder cancer treated with BCG in combination with blinded study product (one of two doses of vesigenurtacel-L or placebo)
- Arm 4: To evaluate 1-year disease-free survival in patients with non-muscle invasive bladder cancer treated with high dose vesigenurtacel-L monotherapy

2.2 Secondary Objectives

- To evaluate the safety of the combination of vesigenurtacel-L and BCG (Phase 2 only)
- To evaluate the safety of high dose vesigenurtacel-L monotherapy (Phase 2 only)
- To evaluate the proportion of patients with recurrence at 3, 6, 12, 18, and 24 months
- To evaluate the proportion of patients with progressive disease at 3, 6, 12, 18, and 24 months
- To evaluate disease-free survival at 3, 6, 18, and 24 months
- To evaluate overall disease-free survival
- To evaluate overall survival (OS)
- To evaluate the proportion of patients undergoing post-treatment TURBT or fulguration by 12 and 24 months
- To evaluate the proportion of patients undergoing cystectomy by 12 and 24 months
- To evaluate the proportion of patients with immunologic response of PBMCs via intracellular cytokine staining (ICS) by flow cytometry and/or ELISPOT on CD8+ cells following vesigenurtacel-L vaccination

2.3 Exploratory Objectives

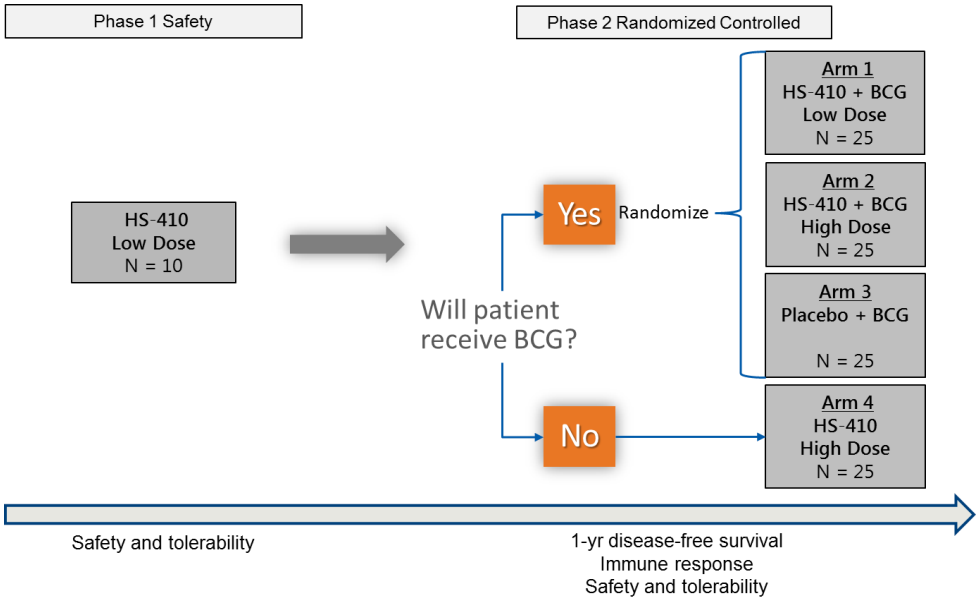
- Immunologic response of PBMCs (analysis of surface markers, CD3, CD4, CD8, CD19, CD25, CD45, CD56, FoxP3, and degranulation) and stimulation analysis via ICS of IFNγ and granzyme B (gzB)
- Total PBMC counts by flow cytometry, including lymphocyte subsets (B cells, helper T-cells, cytotoxic T-cells, NK cells and T-reg)
- Evaluation of tumor tissue obtained prior to treatment for antigen expression, expression of major histocompatibility complex (MHC) class I, and expression of immunosuppressive molecules
- Evaluation of tumor tissue obtained from repeat biopsy, if clinically indicated, for presence of tumor infiltrating T-lymphocytes (TILs)
- T cell receptor sequencing of PBMCs and tumor tissue to determine correlation between clonally expanded T cell populations and other endpoints
- Immune cell infiltration and inflammatory cytokine levels in urine (Phase 2 only)

3.0 TRIAL DESIGN

3.1 Study Design Overview

This is a multi-center, randomized, placebo-controlled study consisting of two phases as shown in Figure 1 below.

Figure 1. Study Design



Patients with non-muscle invasive bladder cancer who have either undergone TURBT or fulguration for the removal of papillary disease or who have carcinoma in situ (CIS) only, are candidates for BCG treatment, and are judged to be at an increased risk for recurrence are eligible if they are BCG naive or have completed previous BCG treatment >12 months prior to the baseline staging procedure. Phase 2 also allows patients who will not otherwise receive BCG.

The Phase 1 portion is an open-label, safety study consisting of one cohort with 10 patients. Patients will have previously received 3-6 instillations of weekly intravesical BCG induction therapy (as standard of care) followed by low dose intradermal (1×10^6 cells) vesigenurtacel-L monotherapy.

In Phase 2, patients will be assigned to treatment groups based on whether they will receive induction BCG in the typical post-TURBT window. If the investigator plans to administer BCG, patients will be randomized to one of three blinded (physician-patient), placebo-controlled groups and receive either intradermal placebo or low dose or high dose (1×10^7 cells) vesigenurtacel-L in combination with induction and maintenance intravesical BCG. If patients will not receive BCG, they will be enrolled into an open-label, non-randomized group and receive high dose intradermal vesigenurtacel-L monotherapy.

Phase 1: Patients enrolled in the first cohort within 8-10 weeks of TURBT or fulguration for patients with papillary disease and staging procedure for patients with CIS only and after induction BCG will be treated with vesigenurtacel-L weekly for 6 weeks. After a one-week vaccine holiday for disease assessment, patients will receive vesigenurtacel-L for an additional 6 weeks followed by three once monthly treatments for a total of 15 vaccinations. Patients will be observed weekly to assess the safety of vesigenurtacel-L. Dosing of the first three patients will be staggered by two-week intervals to allow for safety evaluation before treating additional patients. If vesigenurtacel-L appears safe and well-tolerated in the 3 lead-in patients, dosing will be continued to 10 patients.

Phase 2: Dosing in Phase 2 will begin when all 10 patients have been dosed in the Phase 1 cohort, at least 6 patients in that cohort have completed the Week 7 safety assessments, and the Data Monitoring Committee (DMC) has met to review this data and agreed it is safe to advance to Phase 2. A total of 100 patients will be assigned to four groups: 75 who will receive BCG will be randomized to arms combining either low dose vesigenurtacel-L, high dose vesigenurtacel-L, or placebo, respectively, with induction and maintenance BCG; 25 who will not receive BCG will be enrolled in the high dose vesigenurtacel-L monotherapy arm.

In the randomized arms, treatment will commence within 6 weeks of the most-recent TURBT or fulguration for patients with papillary disease and staging procedure for patients with CIS only. Patients will be treated during an induction phase with weekly intravesical BCG and intradermal blinded study product (vesigenurtacel-L or placebo) for 6 weeks followed by 6 weekly injections of blinded study product alone. During a subsequent maintenance phase, patients will receive an additional three courses of three once-weekly blinded study product injections in combination with intravesical BCG approximately 3, 6, and 12 months after initiating induction BCG. Patients may receive additional courses of maintenance BCG in long-term follow-up at the investigator's discretion but should not receive any other cancer therapy prior to disease recurrence/progression.

In the monotherapy arm, treatment will commence within 6 weeks of the most-recent TURBT or fulguration for patients with papillary disease and staging procedure for patients with CIS only. Patients will be treated during an induction phase with weekly intradermal vesigenurtacel-L for 12 weeks. During a subsequent maintenance phase, patients will receive an additional three courses of three once-weekly vesigenurtacel-L injections approximately 3, 6, and 12 months after initiating induction vesigenurtacel-L.

All patients in both the Phase 1 and Phase 2 portions of the study will have a cystoscopy and cytology and, if clinically indicated, a biopsy performed approximately every 3 months for 2 years then every 6 months for up to a year, study termination, disease progression, or recurrence requiring treatment discontinuation, whichever occurs first. Patients with evidence of disease at an assessment may continue on treatment if judged by the investigator to be in the patient's best interest (e.g. would normally receive another course of BCG therapy as standard of care (SOC)). Upon discontinuation of study treatment, additional treatment will be at the discretion of the treating physician per SOC. While treatment may continue in the presence of evidence of disease, statistical analysis of disease-free status will still follow strict definitions as defined in section 10.1 Evaluation of Disease.

3.2 Justification of Study Product Administration Strategy

A clinical trial of a similar vaccine for lung cancer derived from the same proprietary technology as the vaccine for this study examined three dosing schedules: twice weekly, weekly, and once every two weeks. The twice weekly and weekly dosing schedules were determined to produce the most desirable immune response in peripheral blood (at least a doubling of CD8 from baseline). The weekly dosing schedule was selected for this trial as it was determined to provide reasonable patient acceptability for frequency of treatment visits and concordance with the standard BCG dosing schedule.

Two doses were selected (1×10^6 cells and 1×10^7 cells) for this study. The 1×10^7 cell dose was selected based on the number of cells needed to produce an equivalent amount of gp96-Ig to that used in the lung cancer vaccine. Additionally, murine data suggest that lower doses may produce a sufficient immune

response and may even result in superior clinical effects, and therefore, the lower dose of 1 x 10^6 cells was included as one of the two doses for evaluation in this trial.

Study product will be administered weekly as the number of intradermal injections required to reach the number of cells per dose with no more than 0.1mL per injection (see Section 8.3). The selection of the route of administration is based on the hypothesis that split doses stimulate stronger immune responses by allowing vaccine antigens to reach more regional lymph nodes (where immune responses are generated). Vesigenurtacel-L will be administered intradermally to enhance stimulation of cellular immune responses as compared to subcutaneous or intramuscular immunization.

3.3 Number of Subjects

Approximately 110 patients will be enrolled from up to 20 clinical trial centers. In Phase 1, 10 patients will be enrolled in a single cohort given treatment with monotherapy low dose vesigenurtacel-L. In Phase 2, 25 patients will be enrolled in each of four arms: low dose vesigenurtacel-L in combination with BCG, high dose vesigenurtacel-L in combination with BCG, placebo in combination with BCG, and high dose vesigenurtacel-L monotherapy (100 patients total).

3.4 Study Endpoints

3.4.1 Primary Efficacy Endpoint

Phase 1: Safety and tolerability

Phase 2: 1-year Disease-Free Survival (1-yr DFS)

3.4.2 Secondary Endpoints

- Safety of the combination of vesigenurtacel-L and BCG (Phase 2 only)
- Safety of high dose vesigenurtacel-L monotherapy (Phase 2 only)
- Proportion of patients with recurrence at 3, 6, 12, 18, and 24 months
- Proportion of patients with progressive disease at 3, 6, 12, 18 and 24 months
- Disease-free survival (DFS) at 3, 6, 18, and 24 months
- Overall DFS
- Overall Survival (OS)
- Proportion of patients undergoing post-treatment TURBT or fulguration by 12 and 24 months
- Proportion of patients undergoing cystectomy by 12 and 24 months
- Proportion of patients with immunologic response of PBMCs via intracellular cytokine staining (ICS) by flow cytometry and/or ELISPOT on CD8+ cells after receiving vesigenurtacel-L treatment as compared to baseline

3.4.3 Exploratory Endpoints

- Immunologic response of PBMCs (analysis of surface markers, CD3, CD4, CD8, CD19, CD25, CD45, CD56, FoxP3, and degranulation) and stimulation analysis via ICS of IFNγ and gzB
- Total PBMC counts by flow cytometry, including lymphocyte subsets (B cells, helper T-cells, cytotoxic T-cells, NK cells and T-reg)

- Evaluation of tumor tissue obtained prior to treatment for antigen expression, expression of major histocompatibility complex (MHC) class I, and expression of immunosuppressive molecules by mRNA expression and/or immunohistochemical analysis
- Evaluation of tumor tissue obtained from repeat biopsy, if clinically indicated, for presence of infiltrating T-lymphocytes (TILs)
- T cell receptor sequencing of PBMCs and tumor tissue to determine correlation between clonally expanded T cell populations and other endpoints
- Immune cell infiltration and inflammatory cytokine levels in urine (Phase 2 only)

3.5 Study Termination Criteria

The sponsor may terminate the study at any time on the basis of safety considerations or other factors that may be deemed to affect the scientific validity or ethical viability of the protocol.

4.0 PARTICIPANT SELECTION

4.1 Inclusion Criteria

Patients must meet all of the following inclusion criteria to be enrolled into the study:

1. Willing and able to sign informed consent and comply with the protocol, including clinic visits to receive weekly vesigenurtacel-L injections for 12 doses followed by either monthly vesigenurtacel-L injections for three months in Phase 1 or three courses of three once-weekly injections in Phase 2.

2. Histologically or cytologically confirmed non-muscle invasive bladder cancer [Ta, T1 or Tis (CIS)]. Papillary disease must have been removed by transurethral resection or fulguration.

3. Either

   i. High-risk disease, defined as T1 and/or high-grade and/or CIS, *or*

   ii. Intermediate-risk disease defined as Ta low-grade with at least three of the following four risk factors: multiple tumors, tumor size > 3cm, early recurrence (<1 year from previous staging procedure), or recurrence with a frequency of more than once in any 12 month period.

4. Patients must be BCG naive or have completed previous BCG treatment >12 months prior to the baseline staging procedure.

5. For Phase 2 only: Arms 1, 2, and 3: Suitable, in the opinion of the investigator, to receive a 6-week course of induction intravesical BCG in the adjuvant setting within 6 weeks following the baseline staging procedure for the current occurrence of non-muscle invasive bladder cancer. Arm 4: Suitable for monotherapy vaccine administration post-TURBT. For Phase 1 only: Has previously received 3-6 weekly doses of BCG.

6. Age ≥18 years

7. Lab parameters:

- Albumin ≥2.5 mg/dL
- Total bilirubin <1.5 mg/dL
- Alanine transaminase (ALT) and aspartate transaminase (AST) ≤2.5 × upper limit of normal (ULN)
- Serum creatinine ≤2.2 mg/dL or calculated creatinine clearance >35 mL/minute per the Cockcroft-Gault formula
- White blood cell (WBC) count ≥4,000/mm^3 with an absolute neutrophil count ≥1,500/mm^3
- Hemoglobin ≥9 g/dL
- Platelet count ≥75,000/mm^3

8. Women of childbearing potential or men of fathering potential must use adequate birth control measures (e.g., abstinence, oral contraceptives, intrauterine device, barrier method with spermicide, or surgical sterilization) during the study and for 6 months after receiving the last administration of study medication. Female patients of childbearing potential must test negative for pregnancy prior to enrolling in the trial.

4.2 Exclusion Criteria

Patients that meet any of the following exclusion criteria are not eligible to be enrolled into the study:

1. Known human immunodeficiency virus (HIV) infection or other immunodeficiency disorders, either primary or acquired
2. Infections or concurrent illness, requiring active therapy
3. Any condition requiring active steroid or other immunosuppressive therapy
4. Active malignancies within 12 months with the exception of those with a negligible risk of metastasis or death treated with expected curative outcome
5. Prior prostatic pelvic radiation within the past 12 months
6. Known history of clinically significant cardiac impairment, congestive heart failure > New York Heart Association (NYHA) cardiac disease classification Class II, unstable angina, or myocardial infarction during the previous three months
7. Known current alcohol or chemical abuse, or mental or psychiatric condition precluding compliance with the protocol
8. Pregnant or nursing
9. Known allergy to soy, egg, or peanut products
10. Receiving another investigational agent (30 day wash-out required prior to first dose)
11. Neo-adjuvant therapy prior to the baseline staging procedure for the current occurrence of non-muscle invasive bladder cancer
12. Prior treatment with a cancer vaccine for this indication

13. Prior vaccination with BCG for tuberculosis disease

14. Prior splenectomy

5.0 SAFETY MONITORING

5.1 Data Monitoring Committee

A study specific Data Monitoring Committee (DMC) will provide dose expansion recommendations during Phase 1 and will continue safety surveillance in Phase 2. A full description of the membership, role, and responsibilities of the DMC will be outlined in a separate charter.

5.1.1 Phase 1

A lead-in phase will enroll three patients in Phase 1 at the low dose of vesigenurtacel-L (1 x 10^6 cells). Patients will be observed weekly to assess the safety of vesigenurtacel-L. Dosing of the first three patients will be staggered by two-week intervals to allow for safety evaluation before treating additional patients. The DMC will convene after the third patient has received at least two doses of vesigenurtacel-L and at least one patient has completed the Week 7 safety assessments. If vesigenurtacel-L appears safe and well-tolerated in the 3 lead-in patients, dosing will be continued to 10 patients.

The DMC will reconvene when all 10 patients in Phase 1 have received vesigenurtacel-L and data is available for the Week 7 safety assessments from at least 6 patients. If this regimen is determined to be safe by the DMC, Phase 2 will commence.

5.1.2 Phase 2

In order to continually monitor safety during the Phase 2 portion, the DMC will review (unblinded) all available safety data after one patient has been randomized to each of the active arms and has completed four weeks of treatment and then after 3, 6, and 12 patients in each randomized treatment group have completed the Week 7 assessment. Subsequently the DMC will review all available safety data at regular three-monthly intervals until study completion or should they determine that review is no longer necessary. Additionally, the DMC will convene on an ad-hoc basis should any patient experience a Grade 3 or higher adverse event (considered by the investigator to be related to vesigenurtacel-L) at any time during the study. Depending on emerging data, the DMC will have the authority to suspend allocation to a particular study treatment and require that additional patients are studied in a particular arm or at a particular dose level of vesigenurtacel-L, in order to further characterize the safety profile.

5.2 Dose Limiting Toxicities and Stopping Rules

5.2.1 Dose Limiting Toxicities

Dose limiting toxicities (DLT) (i.e. toxicities which would prevent an escalation to a higher dose in Phase 2) will be evaluated by the DMC during Phase 1 of the trial. The period for evaluating DLTs will be from the time of administration of the first dose of vesigenurtacel-L until the time that all 10 patients in Phase 1 have received at least one dose of vesigenurtacel-L and at least 6 patients have received 6 doses. A DLT is

defined as any anaphylactic reactions, a full-thickness ulceration/necrosis, or any AE ≥ Grade 3 related to study product with the following exceptions:

- Local injection site reactions lasting <72 hours including pain, redness, swelling, induration, or pruritus
- Systemic reactions lasting <72 hours of fever, myalgia, headache, or fatigue

Grading of DLTs will be according to the National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Event (CTCAE) v 4.03.

If one patient in Phase 1 experiences a DLT prior to the dose expansion decision to move to Phase 2, escalation may still be considered; if more than one patient experiences a DLT , expansion will not occur.

5.2.2 Trial Stopping Rules

In the event of a death within 24 hours of vaccination that cannot be clearly attributed to another cause, or ≥3 related SAEs (in any number of patients) at any time after receiving study product during the treatment period, dosing will halt immediately, and the DMC will be consulted. All data will be reviewed prior to any further dosing, and dosing will not continue until the DMC agrees that it is safe to continue. At the discretion of the DMC, the Food and Drug Administration (FDA) or other Health Regulatory Agencies may be consulted.

5.3 Emergency Unblinding of Treatment Assignment

Investigational product for this study has been packaged and labeled in a blinded fashion. Although the vial labels will be blinded in Phase 1 of the trial, the patient and the study personnel will know the dose the patient is receiving, since the Phase 1 portion of the trial is not blinded. For the Phase 2 portion of the trial, patients in Arms 1-3 will be randomized to vesigenurtacel-L (high dose or low dose) or placebo. The patient and site personnel will not know which treatment the patient is receiving. For Arm 4, however, patients and study personnel will know the treatment the patient is receiving.

Unblinding a treatment assignment for adverse events should only be performed in situations where knowledge of the treatment assignment is essential for further medical management of the patient. Unblinding can only be done by the study medical monitor. When unblinding is necessary, the investigator should contact the study medical monitor to discuss. All unblinding events will be recorded and reported by the IWRS. Specific steps for requesting unblinding will be provided in the Study Procedures Manual.

6.0 STUDY PROCEDURES

A signed, written informed consent form that is currently approved by an IRB must be obtained from the potential patient before he/she can participate in any study-specific procedures, including screening procedures.

Patients will be enrolled (Phase 1 and Arm 4 of Phase 2) and randomized (Arms 1-3 of Phase 2) once all screening procedures have been completed and it is determined that the patient meets all eligibility criteria. The schedule of assessments is distinct for patients receiving low dose vesigenurtacel-L monotherapy in Phase 1 and for patients receiving blinded study product (vesigenurtacel-L or placebo) in

combination with BCG or high dose vesigenurtacel-L monotherapy in Phase 2. These two different schedules are outlined below.

6.1 Phase 1

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6.1.1 Phase 1 Schedule of Events

Procedure	Screening	Baseline	Week 1[3]	Weeks 2-6[4]	Week 7	Weeks 8-13[4]	Week 14	Week 17	Week 21	Week 25	Week 29 (EOT)[5]	Long-term Follow-up
Study Day	≤ -4 wks.	-3 to 1	1		43 (±1)		92 (±1)	113 (±3)	141 (±3)	169 (±3)	197 (±3)	Q3mos. 2 yrs; Q6mos. 3rd yr
Baseline Documentation												
Informed Consent	X											
Verify All Eligibility Criteria	X											
Enrollment		X										
Medical History	X[1]	X										
Physical Exam[6]	X	X[2]			X		X				X	
Pathology Review	X											
12-lead ECG	X				X		X				X	
Laboratory Studies												
Immunologic Response[7]		X			X		X				X	
Hematology, Chemistry and LDH, Dipstick Urinalysis	X[1]	X[2]			X		X		X		X	
Pregnancy Test (urine or serum)	X[1]	X[2]									X	
Autoimmune Labs[8]		X					X				X	
Tumor Assessments												
Cystoscopy/Cytology for disease recurrence per SOC[9]					X				X			X[13]
Tumor collection for antigen screen			X									
Dosing												
Vesigenurtacel-L Administration[10]			X	X		X		X	X	X		
Other Clinical Assessments												
Autoimmune Phenomena[11]		X					X				X	
Adverse Events[12]			X	X	X	X	X	X	X	X	X	
Concomitant Medications	X[1]	X	X	X	X	X	X	X	X	X	X	
Survival and subsequent therapy												X

[1] Screening evaluations should be completed ≤2 weeks of first dose.

[2] PE, hematology, chemistry, LDH, dipstick urinalysis and pregnancy test do not need to be repeated at Baseline if they were performed at Screening within three days prior to first dose.

[3] First vesigenurtacel-L dose should occur 8-12 weeks (56-84 days) following TURBT or fulguration for patients with papillary disease and staging procedure for patients with CIS only regardless of the number of BCG instillations.

[4] Weekly study evaluations should be completed within ±1 day of the target visit date.

[5] EOT evaluations should be completed 4 weeks ±3 days after last dose of study vesigenurtacel-L or early discontinuation of study treatment.

[6] PE at screening and Week 29 (End of Treatment) will have a full examination of body systems and vital signs. Other PE evaluations will be limited to symptoms, weight and vital signs.

[7] 70mL of heparinized blood and 10mL of non-heparinized blood will be collected at the indicated visits.

[8] ANA, TSH, ESR, C-reactive protein are required. Other tests (e.g. RF, T3, T4, thyroid antibodies) will be performed only as clinically indicated.

[9] All patients will have a cystoscopy/cytology performed at Week 7 and at Week 21. If clinically indicated, a repeat biopsy will be performed. Patients with evidence of disease at an assessment may continue on treatment if judged by the investigator to be in the patient's best interest (e.g. would normally receive another course of BCG therapy as SOC). Upon discontinuation of study treatment, additional treatment will be at the discretion of the treating physician, and patients will continue in long-term follow-up on the study.

[10] Vesigenurtacel-L is administered weekly x 6 weeks to all patients. Patients continuing on trial will receive 6 additional weekly vaccinations then monthly x 3 months. Each dose will be divided into the number of intradermal injections required to reach $1x10^6$ cells per dose with no more than 0.1 mL per injection (approximately 4-6 injections). Patients should remain on site for 30 minutes following each vaccination for observation of adverse events.

[11] Includes eye exam for dry eyes, lymph node and joint assessment, and skin exam for vitiligo and rashes.

[12] AEs should be recorded from first dose through four weeks following the last dose of study medication regardless of the causal relationship to the study medication. AEs considered related to study medication should be recorded at any time regardless of when they occurred.

[13] Cystoscopy/Cytology for disease recurrence per SOC (approximately every 3 months for 2 years then every 6 months for up to a year). Patients who are determined to have evidence of disease will have SOC treatment per the discretion of the investigator and will continue in long-term follow-up on the study.

6.1.2 Phase 1 Screening Procedures

The following procedures must be conducted ≤4 weeks prior to the first dose of vesigenurtacel-L:

- Written informed consent
- Verify eligibility criteria
- Patient demographics
- Pathology Review
    - Verification of Bladder Cancer Staging at the time of the most recent staging procedure (refer to Appendix 1.) *High-risk or intermediate-risk non-muscle invasive disease must be histologically/cytologically confirmed. There will be no central pathology review. In the event that multiple procedures are performed for this occurrence of disease, dates of all procedures will be captured.*
    - Verification of documentation of cancer sub-type (transitional cell carcinoma, squamous cell carcinoma, adenocarcinoma or undifferentiated carcinoma)
- Physical examination (including weight, vital signs [heart rate, temperature, respiratory rate and blood pressure])
- 12-lead electrocardiogram (ECG)

The following procedures must be conducted ≤2 weeks prior to the first dose of vesigenurtacel-L:

- Medical history, including concomitant medications within 14 days of first dose
- Hematology, chemistry with LDH, and dipstick urinalysis
- Urine or serum pregnancy test for female patients of childbearing potential

6.1.3 Phase 1 On-Study Procedures

Study-related procedures and assessments performed during treatment on study are detailed as follows and in the Schedule of Events table (see Section 6.1.1).

6.1.3.1 Phase 1 Baseline Assessments (Day -3 to Day 1)

The following activities may be performed within three days of enrollment or on Day 1 prior to dosing:

- Update of medical history, including concomitant medications
- Blood draw for immune monitoring
- Physical examination (symptoms, weight, vital signs only if screening exam performed more than three days prior to first dose)
- Hematology, serum chemistry, urinalysis (unless screening labs obtained within three days of first dose)
- Urine or serum pregnancy test for female patients of childbearing potential (unless screening labs obtained within three days of first dose)
- Autoimmune Labs (ANA, TSH, ESR, and C-reactive protein are required; RF, T3, T4, and thyroid antibodies if clinically indicated)
- Assessment of adult autoimmune system disorders (including: eye exam for dry eyes, lymph node and joint assessment for swelling, and skin exam for vitiligo and rash)

Once the patient has met all of the eligibility requirements for the study, the patient will receive the treatment assignment from IWRS. Each patient will be considered enrolled in the study at the time of treatment assignment.

6.1.3.2 Phase 1 Assessments at Week 1 (Day 1)

The following procedures will be performed after all the previous baseline procedures have been completed.

- Study product administration
    - Initiate series of weekly vesigenurtacel-L dosing
- Monitor patients on site for potential acute reactions for 30 minutes after vesigenurtacel-L administration
- Record adverse events
- Send at least 4, non-stained, 10 micron sections from most recent staging procedure for evaluation of antigen expression. If slides are not available, formalin-fixed paraffin embedded (FFPE) tissue (≥50 microns) is also acceptable.

6.1.3.3 Phase 1 Assessments at Week 2 (Day 8) through Week 6 (Day 36)

The following procedures will be performed at each of the weekly visits for Week 2 (Day 8 ±1), Week 3 (Day 15±1), Week 4 (Day 22±1), Week 5 (Day 29±1), and Week 6 (Day 36±1):

- Study product administration
    - Weekly vesigenurtacel-L dosing
- Monitor patients on site for potential acute reactions for 30 minutes after vesigenurtacel-L administration
- Record adverse events
- Record concomitant medications

6.1.3.4 Phase 1 Assessments at Week 7 (Day 43±1)

The following procedures will be performed at this visit:

- Physical exam (symptoms, weight and vital signs only)
- 12-lead ECG
- Blood draw for immune monitoring
- Hematology, serum chemistry, urinalysis
- Cystoscopy/Cytology and if indicated, a repeat biopsy – per SOC to evaluate for evidence of disease. *Note: Patients with evidence of disease may continue on treatment if judged by the investigator to be in the patient's best interest. Patients who discontinue study treatment will continue in long-term follow-up. If biopsy was performed; provide at least 4, non-stained, 10 micron sections for TCR sequencing and analysis of infiltrating T-cells. If slides are not available, FFPE tissue (≥50 microns) is also acceptable.*
- Record adverse events
- Record concomitant medications

6.1.3.5 Phase 1 Assessments at Week 8 (Day 50) through Week 13 (Day 85)

The following procedures will be performed at each of the weekly visits for Week 8 (Day 50 ±1), Week 9 (Day 57 ±1), Week 10 (Day 64±1), Week 11 (Day 71±1), Week 12 (Day 78±1), and Week 13 (Day 85±1):

- Study product administration
    - Weekly vesigenurtacel-L dosing
- Monitor patient on site for potential acute reactions for 30 minutes after vesigenurtacel-L administration
- Record adverse events
- Record concomitant medications

6.1.3.6 Phase 1 Assessments at Week 14 (Day 92 ±1)

The following procedures will be performed at this visit:

- Physical examination (symptoms, weight, vital signs only)
- Blood draw for immune monitoring
- 12-lead ECG
- Hematology, serum chemistry, urinalysis
- Autoimmune Labs (ANA, TSH, ESR, and C-reactive protein; RF, T3, T4, and thyroid antibodies if clinically indicated)
- Assessment of adult autoimmune system disorders (including: eye exam for dry eyes, lymph node and joints assessment for swelling, and skin exam for vitiligo and rash)
- Record adverse events
- Record concomitant medications

6.1.3.7 Phase 1 Assessments at Week 17 (Day 113 ±3)

The following procedures will be performed at this visit:

- Study product administration
    - Start series of monthly vesigenurtacel-L dosing
- Monitor patient on site for potential acute reactions for 30 minutes after vesigenurtacel-L administration
- Record adverse events
- Record concomitant medications

6.1.3.8 Phase 1 Assessments at Week 21 (Day 141 ±3)

The following procedures will be performed at this visit:

- Cystoscopy/Cytology and if indicated, a repeat biopsy – per SOC to evaluate for recurrent disease. *Note: Patients with evidence of disease may continue on treatment if judged by the investigator to be in the patient's best interest. Patients who discontinue study treatment will continue in long-term follow-up. If biopsy was performed; provide at least 4, non-stained, 10 micron sections for*

TCR sequencing and analysis of infiltrating T-cells. If slides are not available, FFPE tissue (≥50 microns) is also acceptable.

- Hematology, serum chemistry, urinalysis
- Study product administration
    - Monthly vesigenurtacel-L dosing
- Monitor patient on site for potential acute reactions for 30 minutes after vesigenurtacel-L administration
- Record adverse events
- Record concomitant medications

6.1.3.9 Phase 1 Assessments at Week 25 (Day 169 ±3)

The following procedures will be performed at this visit:

- Study product administration
    - Final monthly vesigenurtacel-L dosing
- Monitor patient on site for potential acute reactions for 30 minutes after vesigenurtacel-L administration
- Record adverse events
- Record concomitant medications

6.1.3.10 Phase 1 Week 29 (Day 197 ±3) – End of Treatment Visit (4 weeks post last dose)

The following procedures should be completed approximately four weeks following last dose of vesigenurtacel-L, including patients who discontinue vesigenurtacel-L dosing prematurely.

- Physical exam (full examination as well as weight and vital signs)
- 12-lead ECG
- Blood draw for immune monitoring
- Hematology, serum chemistry, urinalysis
- Urine or serum pregnancy test for female patients of childbearing potential
- Autoimmune Labs (ANA, TSH, ESR, and C-reactive protein are required; RF, T3, T4, and thyroid antibodies if clinically indicated)
- Assessment of adult autoimmune system disorders (including: eye exam for dry eyes, lymph node and joint assessment for swelling, and skin exam for vitiligo and rash)
- Record concomitant medications
- Record adverse events

6.2 Phase 2

6.2.1 Phase 2 Schedule of Events

Procedure	Screen	Baseline	Week 1[3]	Weeks 2-6[4]	Week 7	Weeks 8-12[4]	Week 13	Weeks 14-16[4]	Week 25	Weeks 26-27[16]	Week 28	Week 37	Week 49	Weeks 50-52[16]	Week 56 (EOT)[5]	Long-term Follow-up
Study Day	≤ -4 wks.	-3 to 1	1		43 (±1)		85 (±1)		169 (±3)		190 (±3)	253 (±3)	337 (±3)		386 (±3)	Q3mos. 2yrs; Q6mos. 3rd yr
Baseline Documentation																
Informed Consent	X															
Verify All Eligibility Criteria	X															
Enrollment/Randomization		X														
Medical History	X[1]	X														
Physical Exam[6]	X	X[2]					X								X	
Pathology Review	X															
12-lead ECG	X														X	
Laboratory Studies																
Immunologic Response[7]		X			X[14]		X				X[14]				X	
Hematology, Chemistry and LDH, Dipstick Urinalysis	X[1]	X[2]					X		X			X	X		X	
Pregnancy Test (urine or serum)	X[1]	X[2]													X	
Autoimmune Labs[8]		X													X	
Tumor Assessments																
Cystoscopy/Cytology for disease recurrence per SOC[9]							X		X			X	X			X[15]
Tumor collection for antigen screen			X													
Dosing																
Study Product Administration[10]			X	X	X	X		X		X	X			X		
BCG Administration[11]			X	X				X		X	X			X		
Other Clinical Assessments																
Autoimmune Phenomena[12]		X					X								X	
Adverse Events[13]			X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant Medications	X[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Survival and subsequent therapy																X

[1] Screening evaluations should be completed ≤ 2 weeks of first dose.

[2] PE, hematology, chemistry, LDH, dipstick urinalysis and pregnancy test do not need to be repeated at Baseline if they were performed at Screening within three days prior to first dose.

[3] First dose of study product should occur within 6 weeks of baseline staging procedure.

[4] Weekly study evaluations should be completed within ±1 day of the target visit date.

[5] EOT evaluations should be completed 4 weeks ±3 days after last dose of study product or early discontinuation of study treatment.

[6] PE at screening and Week 56 (End of Treatment) will have a full examination of body systems and vital signs. Other PE evaluations will be limited to symptoms, weight and vital signs.

[7] 70mL of heparinized blood, 10mL of non-heparinized blood, and 24mL urine will be collected at the indicated visits.

[8] ANA, TSH, ESR, C-reactive protein are required. Other tests (e.g. RF, T3, T4, thyroid antibodies) will be performed only as clinically indicated.

[9] All patients will have a cystoscopy/cytology performed at Week 13. If clinically indicated, a repeat biopsy will be performed. Patients with evidence of disease at an assessment may continue on treatment if judged by the investigator to be in the patient's best interest (e.g. would normally receive another course of BCG therapy as SOC). Upon discontinuation of study treatment, additional treatment will be at the discretion of the treating physician, and patients will continue in long-term follow-up on the study.

[10] For Arms 1-4: Patients will receive study product as the number of intradermal injections required to reach the number of cells per dose with no more than 0.1 mL per injection (approximately 4-6 injections). Patients should remain on site for 30 minutes following each vaccination for observation of adverse events.

[11] For Arms 1-3 only.

[12] Includes eye exam for dry eyes, lymph node and joint assessment and skin exam for vitiligo and rashes.

[13] AEs should be recorded from first dose through four weeks following the last dose of study medication regardless of the causal relationship to the study medication. AEs considered related to study medication should be recorded at any time regardless of when they occurred.

[14] Samples to be collected prior to dosing

[15] Cystoscopy/Cytology for disease recurrence per SOC (approximately every 3 months for 2 years then every 6 months for up to a year). Patients who are determined to have evidence of disease will have SOC treatment per the discretion of the investigator and will continue in long-term follow-up on the study.

[16] Weekly study evaluations should be completed within ±3 days of the target visit date.

6.2.2 Phase 2 Screening Procedures

The following procedures must be conducted ≤4 weeks prior to the first dose of study product:

- Written informed consent
- Verify eligibility criteria
- Patient demographics
- Pathology Review
    - Verification of Bladder Cancer Staging at the time of the baseline staging procedure (refer to Appendix 1) *High-risk or intermediate-risk non-muscle invasive disease must be histologically/cytologically confirmed. There will be no central pathology review. In the event that multiple diagnostic procedures are performed for this occurrence of disease, dates of all procedures will be captured.*
    - Verification of cancer sub-type (transitional cell carcinoma, squamous cell carcinoma, adenocarcinoma or undifferentiated carcinoma)
    - Verification of the date of baseline staging procedure (must be within 6 weeks)
- Physical examination (including weight, vital signs [heart rate, temperature, respiratory rate and blood pressure])
- 12-lead electrocardiogram (ECG)

The following procedures must be conducted ≤2 weeks prior to the first dose of study product:

- Medical history, including concomitant medications within 14 days of first dose
- Hematology, chemistry with LDH, and dipstick urinalysis
- Urine or serum pregnancy test for female patients of childbearing potential

6.2.3 Phase 2 On-Study Procedures

Study-related procedures and assessments performed during treatment on study are detailed as follows and in the Schedule of Events table (see Section 6.2.1).

6.2.3.1 Phase 2 Baseline Assessments (Day -3 to Day 1)

The following activities may be performed within three days of enrollment/randomization or on Day 1 prior to enrollment/randomization:

- Update of medical history including concomitant medications
- Blood and urine collection for immune monitoring
- Physical examination (symptoms, weight, vital signs only if screening exam performed more than three days prior to first dose)
- Hematology, chemistry with LDH, and dipstick urinalysis (unless screening labs obtained within three days of first dose)
- Urine or serum pregnancy test for female patients of childbearing potential (unless screening labs obtained within three days of first dose)

- Autoimmune Labs (ANA, TSH, ESR, and C-reactive protein are required; RF, T3, T4, and thyroid antibodies if clinically indicated)
- Autoimmune Phenomena – Assessment of adult autoimmune system disorders (including: eye exam for dry eyes, lymph node and joint assessment for swelling, and skin exam for vitiligo and rash)

Once the patient has met all of the eligibility requirements for the study, patients who will receive BCG will be randomized (treatment assigned within IWRS). Each patient will be considered enrolled in the study at the time of first dose.

6.2.3.2 Phase 2 Assessments at Week 1 (Day 1)

The following procedures will be performed after all the previous baseline procedures have been completed:

- Study product administration
  - Initiate series of weekly study product dosing (dosing should begin within 6 weeks of baseline staging procedure)
  - Initiate series of weekly BCG dosing (Arms 1-3 only)
  - Monitor patient on site for potential acute reactions for 30 minutes after study product administration
- Record adverse events
- Record concomitant medications
- Send at least 4, non-stained, 10 micron sections from baseline staging procedure for evaluation of antigen expression. If slides are not available, formalin-fixed, paraffin-embedded (FFPE) tissue (≥50 microns) is also acceptable.

6.2.3.3 Phase 2 Assessments at Week 2 (Day 8) through Week 6 (Day 36)

The following procedures will be performed at each of the weekly visits for Week 2 (Day 8 ±1), Week 3 (Day 15±1), Week 4 (Day 22±1), Week 5 (Day 29±1), and Week 6 (Day 36±1):

- Study product administration
  - Weekly study product dosing
  - Weekly BCG dosing (Arms 1-3 only)
  - Monitor patient on site for potential acute reactions for 30 minutes after study product administration
- Record adverse events
- Record concomitant medications

6.2.3.4 Phase 2 Assessments at Week 7 (Day 43±1)

The following procedures will be performed at this visit:

- Blood and urine collection for immune monitoring collected prior to dosing
- Study product administration
  - Weekly study product dosing

  - Monitor patient on site for potential acute reactions for 30 minutes after study product administration
- Record adverse events
- Record concomitant medications

6.2.3.5 Phase 2 Assessments at Week 8 (Day 50) through Week 12 (Day 78)

The following procedures will be performed at each of the weekly visits for Week 8 (Day 50 ±1), Week 9 (Day 57 ±1), Week 10 (Day 64±1), Week 11 (Day 71±1), and Week 12 (Day 78±1):

- Study product administration
  - Weekly study product dosing
  - Monitor patient on site for potential acute reactions for 30 minutes after study product administration
- Record adverse events
- Record concomitant medications

6.2.3.6 Phase 2 Assessments at Week 13 (Day 85±1)

The following procedures will be performed at this visit:

- Physical exam (symptoms, weight and vital signs only)
- Blood and urine collection for immune monitoring
- Hematology, chemistry with LDH, and dipstick urinalysis
- Cystoscopy/Cytology and, if indicated, a repeat biopsy – per SOC to evaluate for evidence of disease. *Note: Patients with evidence of disease may continue on treatment if judged by the investigator to be in the patient's best interest. Patients who discontinue study treatment will continue in long-term follow-up. If biopsy was performed, provide at least 4, non-stained, 10 micron sections for TCR sequencing and analysis of infiltrating T-cells. If slides are not available, FFPE tissue (≥50 microns) is also acceptable.*
- Autoimmune Phenomena – Assessment of adult autoimmune system disorders (including: eye exam for dry eyes, lymph node and joints assessment for swelling, and skin exam for vitiligo and rash)
- Record adverse events
- Record concomitant medications

6.2.3.7 Phase 2 Assessments at Week 14 (Day 92) through Week 16 (Day 106)

The following procedures will be performed at each of the weekly visits for Week 14 (Day 92 ±1), Week 15 (Day 99 ±1), and Week 16 (Day 106 ±1):

- Study product administration
  - Weekly study product dosing
  - Weekly BCG dosing (Arms 1-3 only)
  - Monitor patient on site for potential acute reactions for 30 minutes after study product administration

- Record adverse events
- Record concomitant medications

6.2.3.8 Phase 2 Assessments at Week 25 (Day 169)

The following procedures will be performed at the visit for Week 25 (Day169±3):

- Hematology, chemistry with LDH, and dipstick urinalysis
- Cystoscopy/Cytology and, if indicated, a repeat biopsy – per SOC to evaluate for recurrent disease. *Note: Patients with evidence of disease may continue on treatment if judged by the investigator to be in the patient's best interest. Patients who discontinue study treatment will continue in long-term follow-up. If biopsy was performed, provide at least 4, non-stained, 10 micron sections for TCR sequencing and analysis of infiltrating T-cells. If slides are not available, FFPE tissue (≥50 microns) is also acceptable.*
- Record adverse events
- Record concomitant medications

6.2.3.9 Phase 2 Assessments at Week 26 (Day 176) and Week 27 (Day 183)

The following procedures will be performed at each of the weekly visits for Week 26 (Day 176±3) and Week 27 (Day 183±3):

- Study product administration
  - Weekly study product dosing
  - Weekly BCG dosing (Arms 1-3 only)
  - Monitor patient on site for potential acute reactions for 30 minutes after study product administration
- Record adverse events
- Record concomitant medications

6.2.3.10 Phase 2 Assessments at Week 28 (Day 190±3)

The following procedures will be performed at this visit:

- Blood and urine collection for immune monitoring collected prior to dosing
- Study product administration
  - Weekly study product dosing
  - Weekly BCG dosing (Arms 1-3 only)
  - Monitor patient on site for potential acute reactions for 30 minutes after study product administration
- Record adverse events
- Record concomitant medications

6.2.3.11 Phase 2 Assessments at Week 37 (Day 253)

The following procedures will be performed at the visit for Week 37 (Day 253±3):

- Hematology, chemistry with LDH, and dipstick urinalysis
- Cystoscopy/Cytology and, if indicated, a repeat biopsy – per SOC to evaluate for recurrent disease. *Note: Patients with evidence of disease may continue on treatment if judged by the investigator to be in the patient's best interest. Patients who discontinue study treatment will continue in long-term follow-up. If biopsy was performed, provide at least 4, non-stained, 10 micron sections for TCR sequencing and analysis of infiltrating T-cells. If slides or curls or fresh frozen specimens are not available, FFPE tissue (≥50 microns) is also acceptable.*
- Record adverse events
- Record concomitant medications

6.2.3.12 Phase 2 Assessments at Week 49 (Day 337)

The following procedures will be performed at the visit for Week 49 (Day 337±3):

- Hematology, chemistry with LDH, and dipstick urinalysis
- Cystoscopy/Cytology and, if indicated, a repeat biopsy – per SOC to evaluate for recurrent disease. *Note: Patients with evidence of disease may continue on treatment if judged by the investigator to be in the patient's best interest. Patients who discontinue study treatment will continue in long-term follow-up. If biopsy was performed, provide at least 4, non-stained, 10 micron sections for TCR sequencing and analysis of infiltrating T-cells. If slides or curls or fresh frozen specimens are not available, FFPE tissue (≥50 microns) is also acceptable.*
- Record adverse events
- Record concomitant medications

6.2.3.13 Phase 2 Assessments at Week 50 (Day 344) through Week 52 (Day 358)

The following procedures will be performed at each of the weekly visits for Week 50 (Day 344±3), Week 51 (Day 351±3), and Week 52 (Day 358±3):

- Study product administration
  - Weekly study product dosing
  - Weekly BCG dosing (Arms 1-3 only)
  - Monitor patient on site for potential acute reactions for 30 minutes after study product administration
- Record adverse events
- Record concomitant medications

6.2.3.14 Phase 2 Week 56 (Day 386 ±3) – End of Treatment Visit (4 weeks post last dose)

The following procedures should be completed approximately four weeks following last dose of study product including patients who discontinue study product dosing prematurely.

- Physical exam (full examination as well as weight and vital signs)
- 12-lead ECG

- Blood and urine collection for immune monitoring
- Hematology, chemistry with LDH, and dipstick urinalysis
- Urine or serum pregnancy test for female patients of childbearing potential
- Autoimmune Labs (ANA, TSH, ESR, and C-reactive protein are required; RF, T3, T4, and thyroid antibodies if clinically indicated)
- Autoimmune Phenomena – Assessment of adult autoimmune system disorders (including: eye exam for dry eyes, lymph node and joint assessment for swelling, and skin exam for vitiligo and rash)
- Record concomitant medications
- Record adverse events

6.3 Long-term Follow-up Visits

All patients will be followed for the procedures listed below every 3 months from the date of the previous visit for 2 years then every 6 months from the date of the previous visit for a year or until study termination, whichever occurs first:

- Survival
- New anticancer treatments initiated after disease recurrence
- TURBT or fulguration procedures
- Cystectomy

In addition patients who have completed all study treatments or have discontinued study product dosing due to reason other than disease recurrence/progression will have the following procedures performed at each long-term follow-up visit:

- Cystoscopy/Cytology; biopsy if area suspicious for disease recurrence is identified at discretion of investigator (*Note: patients who have a biopsy performed will provide at least 4, non-stained, 10 micron sections for TCR sequencing and analysis of infiltrating T-cells.) If slides are not available, FFPE tissue (≥50 microns) is also acceptable.*

If a patient has recurrent/progressive disease and discontinues study treatment, the above disease assessment procedures will be discontinued, and subsequent long-term follow-up visits may be conducted via phone visit.

6.4 Blinding and Minimization of Bias

The Phase 1 portion of the trial will be open label. Ten patients will be enrolled in a single cohort that will receive low dose vesigenurtacel-L vaccine (1×10^6 cells) monotherapy. If well-tolerated, the low dose as well as a higher dose (1×10^7 cells) will be advanced to Phase 2.

The Phase 2 portion of the trial will have three blinded (physician-patient), placebo-controlled arms and one open label arm. The placebo has been formulated with an intralipid suspension to visually resemble the vesigenurtacel-L vaccine. Seventy-five patients who will receive BCG will be randomized to low dose vesigenurtacel-L in combination with BCG, high dose vesigenurtacel-L in combination with BCG, or

placebo in combination with BCG; 25 patients who will not receive BCG will be enrolled in an arm that will receive high dose vesigenurtacel-L vaccine monotherapy.

Blinding in Phase 2 was indicated in order to be able to better facilitate ongoing evaluation of safety.

7.0 SUBJECT COMPLETION AND WITHDRAWAL

7.1 Subject Completion

Patients may continue to receive study treatment until they complete the dosing phase of the study or meet the criteria for treatment discontinuation described in Section 7.2.1.

7.2 Subject Withdrawal from Study

In accordance with International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines, a patient has the right to withdraw from the study at any time for any reason without prejudice to his/her future medical care by the physician or at the institution. The investigator and sponsor also have the right to withdraw patients from the study treatment, as described below or for safety, behavioral, or administrative reasons.

7.2.1 Discontinuation from Study Treatment

Every effort must be made by study personnel to keep patients on study treatment. However, a patient **will** be discontinued prior to completion of the study treatment for any of the following reasons:

- Grade 4 adverse event related to study product (or Grade 3 adverse event at the Principal Investigator's discretion).
- Suspected Unexpected Adverse Drug Reaction, which requires patient unblinding
- Grade 3 or greater allergic reaction or autoimmune reaction
- Progressive disease
- Pregnancy
- Termination of the study by Heat Biologics
- Concurrent illness that prevents further administration of treatment

Patients **may** also be discontinued prior to completion of the study treatment for any of the following reasons:

- Recurrent disease (Patients with recurrent disease at an assessment may continue on treatment if judged by the investigator to be in the patient's best interest.)
- Significant deviation from protocol on the part of the patient (includes lack of compliance)
- Significant protocol violation on the part of the investigator

The explanation of why the patient is discontinuing study treatment should be documented in the ECRF. If the patient discontinues study treatment due to toxicity, "Adverse Event" will be recorded as the primary reason for withdrawal. If a patient is prematurely discontinued from the study at any time due to an AE or

SAE, the patient must be followed until resolution to Grade 2 or less, unless it is unlikely to improve because of underlying disease.

7.2.2 Discontinuation from Study Follow-Up

If a patient prematurely discontinues study treatment for any reason, the patient will continue to be followed for study endpoints, unless consent for this is specifically withdrawn. If the patient withdraws consent for continued follow up, the investigator must make every effort to perform the EOT assessments four weeks following the last dose of study product, even if the patient has initiated other anticancer treatment.

7.2.3 Lost to Follow-Up

If a patient fails to return for the necessary visits or discontinues prematurely from treatment, a genuine effort should be made to determine the reason why. For a patient lost to follow-up there should be at least two documented attempts to contact the patient.

7.2.4 Replacement of Subjects

Patients will not be replaced. A 10% overage of patients has been included in the sample size to allow for patients who discontinue for reasons other than evidence of disease or toxicity or who are missing data.

8.0 INVESTIGATIONAL PRODUCT

All production, formulation, and packaging of the investigational agent will be in accordance with applicable current Good Manufacturing Practice (cGMP) and meet applicable criteria for use in humans.

8.1 Description of Investigational Product, Vesigenurtacel-L

Vesigenurtacel-L is a cell line derived from a human cancer cell line, designated as PC3. The cell line was transfected with the plasmid cDNA 'B45-neo-gp96Ig-HLA A1'. Vesigenurtacel-L has been irradiated to render cells replication incompetent while maintaining biological activity; i.e., expression of certain proteins.

Manufacturing of vesigenurtacel-L includes expansion of batches of cells with testing for presence of expression of HLA-A1 by fluorescence-activated cell sorter and gp96-Ig by enzyme-linked immunosorbent assay (ELISA). Cells are harvested, washed, resuspended in buffer, and irradiated at 12,000 rad.

The vesigenurtacel-L vaccine to be injected will contain irradiated cells expressing HLA-A1 on at least 70% of the cells and produce ≥60ng gp96-Ig/24h x 1 million cells; the cells will have ≥70% viability by trypan blue exclusion.

Vesigenurtacel-L is provided as frozen, single-dose vials either 1) as concentrated frozen liquid, which will require dilution by the pharmacist with sterile saline, or 2) as fully-diluted frozen liquid not requiring additional dilution. In either case the final drug product will consist of cells resuspended in buffered saline containing human serum albumin (HSA), dimethyl sulfoxide (DMSO), and pentastarch and will be delivered at doses of either 1×10^6 cells or 1×10^7 cells. Overfill is factored into each vial to allow extraction of the full dose for patient administration. Refer to the Pharmacy Manual for instructions for preparation and labeling.

8.2 Description of Placebo

A challenge for cell-based immunotherapy is the development of a placebo control that is safe for use in patients and which mimics the appearance and biophysical properties of intact cells in solution. Toward this end, we will utilize a diluted suspension of Intralipid (Baxter), which is FDA approved for use in humans. This Intralipid solution will be diluted to a final concentration of 0.15% in a buffered saline solution also containing HSA, DMSO, and pentastarch, but lacking vesigenurtacel-L cells. This solution closely resembles the appearance and viscosity of the vesigenurtacel-L vials used in the experimental arms of the study.

Intralipid solution is contraindicated in patients with a soy, egg, or peanut allergy.

8.3 Dosage and Administration of Vesigenurtacel-L and Placebo

At each dosing visit for Phase 2, the site must contact the IWRS for assignment of the dose vial. Study product will be administered intradermally. Each dose will be divided into the number of injections required to reach the number of cells per dose with no more than 0.1 mL per injection (approximately 4-6 injections), and administered as spatially divided intradermal injections separated by approximately 4-5 cm in the same extremity to increase volume distribution and enhance antigen presentation to lymph node regions shared with the urinary bladder. Dosing will rotate injection site extremities every four timepoints: antero-lateral left thigh, antero-lateral right thigh, left buttock, and right buttock. Injection sites will be recorded and retained in the patient records. If injection site reactions are reported as an AE, an alternative injection site may be used upon discussion with the sponsor.

Missed doses may be made up depending on the timing of the dosing, after discussion with the sponsor.

8.4 Dosage and Administration of BCG (Phase 2)

A full dose of BCG according to the investigator's standard practice should be administered intravesically, unless dose reductions are deemed appropriate by the investigator to manage toxicity. The induction phase consists of 6 weekly doses, and the maintenance phase includes three once-weekly doses at 3, 6, and 12 months since the start of induction BCG. Patients who receive 5 of 6 induction doses may continue to receive study product and maintenance BCG.

Additional information can be found in the package inserts:
(http://www.fda.gov/downloads/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/UCM310364.pdf and http://www.merck.com/product/usa/pi_circulars/t/tice_bcg/ticebcg_pi.pdf).
Dose reductions will follow those as defined in Section 8.5.2.

8.5 Treatment Assignment

The definitions of the randomized arms relative to the intended intervention to be used in those arms will be as follows:

Phase 1: Vesigenurtacel-L Low Dose: 1 x10^6 cells per dose

Phase 2:

- Arm 1: Vesigenurtacel-L consisting of 1 x 10^6 cells per dose + BCG

- Arm 2: Vesigenurtacel-L consisting of 1 x 10^7 cells per dose + BCG
- Arm 3: Placebo (containing intralipid for blinding, but no cells) + BCG
- Arm 4: Vesigenurtacel-L consisting of 1 x 10^7 cells per dose

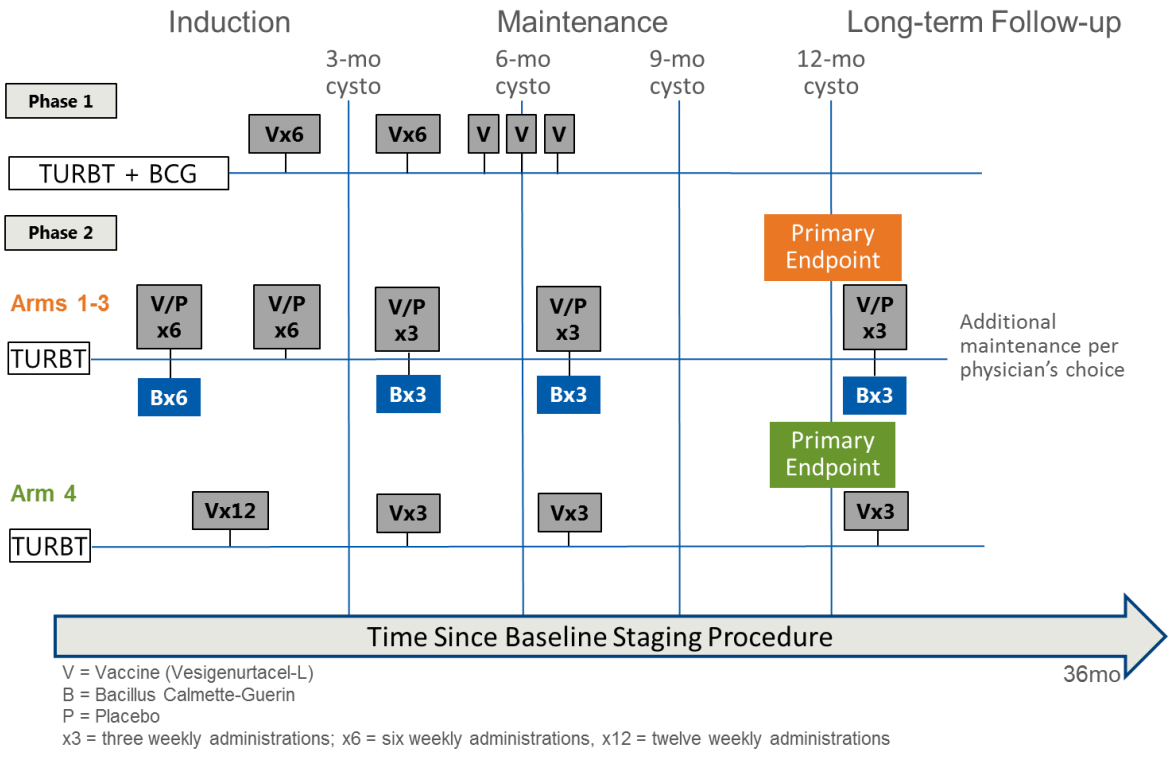
In Phase 2, patients who will receive BCG will be randomized centrally to Arm 1, 2, or 3 using a stratified block design according to risk of recurrence (strata: high vs. intermediate risk) and CIS (strata: yes vs. no). Patients who will not receive BCG will be enrolled in Arm 4.

Due to delays in the batch release of certain doses of vaccine, the randomization schedule may be temporarily revised from a 1:1:1 randomization to a 1:1 randomization, with one arm being briefly suspended. During the period of revised randomization, each patient will maintain at least a 50% chance of receiving vaccine versus placebo. Randomization strata will remain unchanged. Upon batch release of the vaccine the randomization will return to the original 1:1:1 ratio. In order to maintain the study blinding, temporary closure of certain arms will not be disclosed outside of the DMC except as needed for Informed Consent documents.

8.5.1 Schedule and Duration of Treatment

The dose administration will follow the regimen outlined in Figure 2 below.

Figure 2. Dosing Schedule



In Phase 1, each patient will receive intradermal injections of vesigenurtacel-L weekly for 12 doses (doses administered on Weeks 1-6 with a vaccine holiday on Week 7 to allow for disease assessment, followed by Weeks 8-13), then monthly for 3 doses for up to a total of 15 doses, unless the criteria for treatment discontinuation are met. Vesigenurtacel-L should be administered within the allowable windows of the

scheduled dose. In Phase 2, each patient in Arms 1-3 will receive weekly intradermal injections of blinded study product in combination with intravesical induction BCG for 6 weeks followed by 6 weeks of blinded study product monotherapy with a vaccine holiday on Week 13 to allow for disease assessment, followed by three courses of three once-weekly injections in combination with intravesical maintenance BCG for a total of 21 doses, unless the criteria for treatment discontinuation are met. Patients in Arm 4 will receive weekly intradermal injections of vesigenurtacel-L for 12 doses, followed by three courses of three once-weekly injections for a total of 21 doses, unless the criteria for treatment discontinuation are met.

8.5.2 Dose Modifications

Dose modifications of vesigenurtacel-L will not be permitted during the trial.

BCG should be given at full strength with dose reductions as needed for management of toxicity according to the investigator's standard of care.

8.6 Study Product Handling and Accountability

8.6.1 Preparation

Vesigenurtacel-L and placebo must be thawed and labeled prior to injection. In addition, certain batches will require dilution with sterile saline. Preparation of the product and labeling procedures will be described in the Pharmacy Manual.

8.6.2 Labeling

Study product will be labeled with the product name/placebo, the vial number, storage conditions, and other local regulatory requirements.

8.6.3 Storage

Vesigenurtacel-L and placebo must be stored at ≤ -120°C in the vapor phase of a liquid nitrogen dewar. If liquid nitrogen storage is not available at the investigative site, a unit will be supplied by the study sponsor. The sponsor will also arrange for replacement of the liquid nitrogen at regular intervals to ensure that the proper storage temperature is maintained throughout the study.

8.6.4 Product Accountability

The investigator or designee (where applicable) will be responsible for study product accountability, reconciliation, and record maintenance. In accordance with all applicable regulatory requirements, the investigator or designated site staff (e.g., investigational drug pharmacist) must maintain current investigational product accountability records throughout the course of the study. These records will contain the following information:

- Patient Study ID number
- Date, quantity, and vial number of agent received, dispensed, administered, lost, and destroyed
- Documentation of storage conditions

These inventories must be made available for inspection by the study monitor. The investigator will be responsible for ensuring that all used and unused trial supplies are accounted for. At the end of the trial the

study monitor will also collect the investigational agent dispensing record. A copy of the dispensing record should be kept at the site and maintained with the study records.

8.7 Treatment of Investigational Product Overdose

As this is the first patient trial with vesigenurtacel-L, there have been no cases of overdose. Treatment of any suspected or confirmed overdose with vesigenurtacel-L should be symptomatic, and supportive care is recommended in cases where overdose is suspected. As described in the Investigator's Brochure for vesigenurtacel-L, Heat Biologics does not recommend specific treatment for overdose or toxicity; however, the investigator should use appropriate clinical judgment in treating the overdose. For the purposes of this study, an overdose of vesigenurtacel-L is defined as any dose 50% greater than the intended dose for that patient. Appropriate supportive care measures would need to be provided to address these potential toxicities in the event of an overdose.

8.8 Occupational Safety

Precautions should be taken to avoid direct contact with the investigational product. A Material Safety Data Sheet (MSDS) describing occupational hazards and recommended handling precautions will be available to the investigator.

9.0 CONCOMITANT MEDICATIONS AND NON-DRUG THERAPIES

9.1 Permitted Medications and Non-Drug Therapies

A single dose of mitomycin C or other standard intravesical treatment administered immediately post-TURBT (for the current occurrence of non-muscle invasive bladder cancer) is permitted according to the investigative center's standard practice.

Maintenance BCG per the institution's standard of care may be administered to patients in Phase 1 at any time. Additional courses of maintenance BCG may be administered to patients in Phase 2 after the completion of study treatment per the protocol.

All concomitant medications, including prescription and over-the-counter medications, taken during the 14 days before the date of first dose, during the study treatment, and through 4 weeks post the last dose of study product will be documented. Any concomitant medication(s), including herbal or vitamin preparations, taken during the study will be recorded in the ECRF. At a minimum, the drug name, dose, and the dates of administration will be recorded. Caffeine consumption will also be collected.

Local and/or systemic injection reactions may be treated with anti-allergics, antipyretics, and/or analgesics in accordance with standard local practice and investigator's clinical judgment.

Pre-treatment of the vaccine injection site with anesthetic cream is allowed only after the Week 1 vaccine administration has been performed without it and injection pain has been documented as an AE.

Repeat TURBT or fulguration procedures will be permitted only in the setting of persistent, recurrent, or progressive disease according to an investigator's standard practice.

9.2 Prohibited Medications and Non-Drug Therapies

Prohibited concomitant medications include chronic use of systemic corticosteroids or other immunosuppressant medications. Topical and inhalation steroids will be permitted. No concomitant chemotherapy, immunotherapy (other than BCG according to the protocol schedule), immunosuppressive or other anti-cancer therapy will be permitted prior to progression/recurrence or study withdrawal for other reasons.

Administration of other concomitant investigational agents for any indication, other than the vesigenurtacel-L vaccine, is not permitted in the treatment phase of this study and for 30 days prior to first dose.

During long-term follow-up there are no prohibited medications, and patients may enroll in any investigational study for which they are eligible.

9.3 Supportive Care

Patients should receive full supportive care during the study, including transfusions of blood and blood products, and treatment with antibiotics, antiemetics, antidiarrheals, and analgesics, and other care as deemed appropriate, and in accordance with their institutional guidelines. Please see Section 9.2 for prohibited medications.

10.0 ASSESSMENT OF EFFICACY

10.1 Evaluation of Disease

Monitoring for disease status via cystoscopy, cytology, and biopsy if indicated, will be conducted every 3 months during treatment and follow up for 2 years then every 6 months for up to a year per SOC. Disease-free status is defined as no evidence of disease, which in turn is defined as negative cytology, negative cystoscopy, and negative biopsy if clinically indicated.

Recurrence is defined as disease that has recurred to the same extent of disease (i.e. same stage/severity) or to a lower stage/severity of disease compared to screening.

Persistent disease is defined as evidence of CIS disease by 6 months for patients with CIS at screening.

Progression is defined as an increase in T stage from CIS or Ta (at screening) to T1 (lamina propria invasion), development of T2 or greater or lymph node (N+) disease or distant metastasis (M1), or an increase in grade from low to high per the IBCG recommendations.

The stage of disease at the time of recurrence or progression will be captured to distinguish between recurrence to the same extent of disease as at screening (i.e. the same stage/severity) versus recurrence to a lower stage/severity of disease at screening versus persistent disease for CIS versus progression.

The date of confirmation of recurrence or progression is defined as the earliest date on which the diagnosis had been made based on the findings of cystoscopy, urinary cytology, or some other diagnostic imaging technique regardless of whether the patient continues treatment. For the purpose of clarity, in the situation where a patient with CIS documented at screening has evidence of CIS at the 3-month assessment, continues treatment, and still has evidence of CIS at 6 months, that patient will be assumed to have persistent disease from the date of randomization.

For intermediate-risk patients (i.e. without CIS) who have evidence of disease at the 3-month assessment, continue treatment, and still have evidence of disease at 6 months, the date of recurrence would be the date of the 3-month assessment.

If requested, the cystoscopy and cytology reports and images may be appended to the ECRF with all patient identifier information removed and the study site and patient study number written on the report, which is to be signed and dated by the investigator.

10.2 Immunologic Response

Peripheral blood samples and urine specimens will be obtained at time points according to the Schedule of Events. All samples will be shipped to and processed by one or more central laboratories.

Seventy (70) mL heparinized blood and 10 mL of non-heparinized blood will be drawn at each time point and used for analysis as outlined below. Peripheral blood mononuclear cells (PBMCs) will be isolated from heparinized blood samples by Ficoll separation. Isolated PBMCs will be utilized for immunophenotyping analysis using flow cytometry, DNA isolation and subsequent T cell receptor sequencing, intracellular cytokine analysis, and ELISPOT assays as described below. Serum will be collected from non-heparinized blood samples and stored for batch analysis of antibody titers and serum cytokines/chemokines.

Twenty-four (24) mL of urine will be collected at each time point. Part of each sample will be centrifuged and cell counts determined. If there are sufficient numbers of cells, samples may be analyzed by multicolor flow cytometry using standard procedures to examine lymphocyte subsets. The remainder of each sample will be frozen for batch analysis of inflammatory cytokines.

In addition to the analyses specified below, subsequent exploratory mechanistic analyses, the nature of which will be determined by emerging PBMC and tumor biopsy data on the immunological environment pre- and post-vaccine, may also be performed.

10.2.1 Production of Interferon-gamma from CD8+ T Cells (ICS Assay)

The immune response will be evaluated by antigen-specific flow cytometry and/or ELISPOT analysis for IFNγ production by patient T cells. These ICS assays will be done under Good Laboratory Practice (GLP)-like conditions using standard operating procedures and validating assays with standardized negative and positive controls. Processing of all patient samples by a single facility in large batches will be performed to minimize assay variability between samples.

Thawed and isolated PBMCs will be challenged or restimulated with specific tumor vaccine antigens as follows:

- PBMCs alone (negative control)
- PBMCs + PMA + Ionomycin (positive control)
- PBMCs + vesigenurtacel-L whole cell lysates (vaccine)
- PBMC + a cocktail of known shared antigens, including survivin, LAGE-1s, MAGE-A1, and MAGE-A3

A maximum of four stimulation conditions at each time point per blood sample will be set up.

For the flow cytometry assay, following in vitro stimulation, cells will be harvested and labeled with antibodies to cell surface markers, including CD4 and CD8, and then fixed, permeabilized, and stained for the indicated intracellular markers, including IFNγ and gzB. Samples will be analyzed by flow cytometry immediately after staining.

For the ELISPOT assay, the frozen PBMCs will be thawed, antigen challenged, plated for analysis of IFNγ and gzB production by ELISPOT assay, and analyzed in triplicate for each time point for each patient. If cells are limiting, IFNγ analysis will be prioritized. Following incubation, samples will be quantitated in an automated ELISPOT reader.

The frequency of IFNγ producing CD8+ cells is thought to mirror the frequency of cytotoxic CD8+ cells. However, cytotoxicity is primarily mediated by perforin and granzymes following granule exocytosis. In some instances IFNγ secretion and granule exocytosis are uncoupled. Therefore, the direct measurement of gzB secretion by ICS may provide a more direct readout for antigen-specific granule exocytosis and cytotoxicity. For clinical efficiency it may be important to detect both IFNγ secretion and gzB exocytosis. Antigen specificity of the ICS response will be evaluable by comparing responses generated using the various stimulator cell populations and specific shared bladder cancer antigens as indicated. This will also enable separation of the 'allo-antigen' specific response with the potential parent cell line tumor-antigen-specific response. Positive responses will be defined as a greater than two-fold increase in the number of IFNγ positive CD8+ T cells compared to baseline.

10.2.2 PBMC Counts

Total PBMC counts will be obtained from each patient from two sources. First, blood hematology will be performed for each patient at Baseline and the treatment weeks indicated in the Schedule of Events at the clinical centers. Second, the peripheral blood phenotyping analysis (described below) will be performed quantitatively for each of the markers indicated, providing a secondary measure of PBMC subsets defined by expression of the individual markers indicated.

Total PBMC counts may be utilized as a surrogate endpoint for the overall health of a patient's immune system.

10.2.3 Phenotyping of Blood Lymphocyte Subsets

Following alkaline lysis of red blood cells using standard procedures, peripheral blood samples will be stained using antibodies specific for the following cell markers: CD3, CD4, CD8, CD19, CD25, CD45, CD56, and FoxP3. Samples will be analyzed by multicolor flow cytometry using standard procedures.

Flow cytometric analysis of patient peripheral blood samples will quantitatively determine the frequency and number of lymphocytes (CD45+), B cells (CD45+CD3-CD19+), helper T cells (CD45+CD3+CD4+), cytotoxic T cells (CD45+CD3+CD8+), regulatory T cells (CD3+CD4+CD25+FoxP3+), and natural killer cells (CD45+CD56+) at baseline and over the course of therapy. In addition a T cell activation panel (CD4, CD8, Ki67, perforin, IFNγ) will be performed before and after in vitro stimulation with PMA/ionomycin, a regulatory T cell panel (CD4, CD25, FoxP3, CD127, CD45-RA), a myeloid suppressor cell panel (CD39, CD11b, CD124, CD45, HLA-DR, CXCR4), and T cell suppression panel (CD4, CD8, CTLA-4, PD-1, Tim-3) will be performed on freshly isolated PBMC.

10.2.4 TCR Sequencing

ELISPOT and intracellular cytokine assays are frequently used to monitor patient immune response to immunotherapy, despite the knowledge that these assays have not previously been strongly predictive of clinical response. Thus, prognostic immune monitoring assays are highly desired. If T cell receptor (TCR) clones are present that recognize antigens introduced by vesigenurtacel-L, clonal expansion of these cells is indicative of effective vaccination and potentially predictive for the presence of patient-tumor antigen specific T cells.

TCR genomic DNA extracted from tumor tissue and PBMCs will be amplified and sequenced.

The Phase 2 study is designed to explore the feasibility of application of this approach to later phase studies. In addition, data generated using this approach during Phase 2 may later be compiled with a larger data set to investigate the prognostic significance of individual TCR sequences before and during treatment with vesigenurtacel-L.

Although this assay is potentially predictive of a clinical response, it remains an exploratory endpoint in this trial because this analysis can only be confirmed once expansion of individual T cell clones is found to correlate (or not) with improved patient survival. Thus, the TCR sequencing data will be analyzed both before the survival data has matured in order to ascertain whether there are conserved sequences expanded for patients with similar HLA types but also to determine whether a clonal TCR signature emerges that has the potential to be used as a predictive biomarker for response in subsequent trials.

10.2.5 Analysis of Infiltrating T Cells (Post-Treatment Tumor Biopsy)

If a biopsy is performed at any time post-treatment, the tissue will also be examined for presence of infiltrating T-cells (TILs). Two-color fluorescence immunohistochemistry (IHC) and multicolor fluorescence-activated cell sorting analysis will be used for quantification of CD8+ T cells and measurement of their activation status (CD69-expression) and cytotoxic activity (CD107a-expression) *in situ*. These data will be correlated with clinical response.

10.2.6 Antigen Screening of Resected Tumor Tissue

A sample containing at least 4, non-stained, 10 micron sections will be collected for the purpose of screening the tissue for representative antigen expression (LAGE-1, NY-ESO-1, MAGE-[A1-10], CT7, CT10, GAGE, etc.), expression of MHC class I, and expression of immunosuppressive molecules, including, for example, CTLA-4, PD-L1 and PD-1, by mRNA expression and/or IHC analysis. If slides are not available, FFPE tissue (≥50 microns) is also acceptable. These data will be retrospectively correlated with immune response to determine if a particular antigen expression profile may predict response to treatment.

The tumor arrays will be processed by IHC and PCR according to standard methods. Bound antibodies will be visualized by using the avidin-biotin complex method according to the recommendations of the supplier (Vectastatin Elite ABC Kit; Vector Laboratories Inc., Burlingame, CA). Diaminobenzidine will be used as chromogen. 57B staining will be classified as follows: no staining; “weak,” indicating low-intensity staining regardless of positive cell percentages or medium intensity staining of no more than 20% of cells; “moderate,” indicating medium-intensity staining of more than 20% of cells or high-intensity staining of no more than 20% of cells; “strong,” indicating high-intensity staining of more than 20% of cells. Only

moderately and strongly positive cases will be considered positive. For PCR based analysis, total RNA will be isolated from collected tissue samples and reverse transcribed to cDNA using standard methods. The expression of tumor antigens from cDNA samples will then be interrogated using real-time PCR and a variety of specific tumor antigen probes.

11.0 SAFETY ASSESSMENTS

Safety will be assessed throughout the study by a qualified physician, physician assistant, or nursing staff. Measurements used to evaluate safety will include history, physical examination, vital signs, clinical laboratory tests, urinalysis, 12-lead ECG, and monitoring for AEs. AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events Version 4 (NCI-CTCAE v4.03) [NCI, 2010].

Laboratory measurements that deviate significantly (as determined by the investigator) from previous measurements may be repeated. If warranted, additional or more frequent testing than is specified in the protocol should be done to provide adequate documentation of AEs and the resolution of AEs.

11.1 Physical Examination

Medical and physical examinations must be performed by a qualified physician, nurse practitioner, or physician assistant and should include a thorough review of all body systems at Screening, Baseline, and End of Treatment. Examinations should be performed as listed on the schedule of events. Physical examinations will include vital signs (heart rate, temperature, respiratory rate, and blood pressure). Blood pressure, heart rate, and respiration rate will be measured after resting in a semi-supine or supine position, and patients must be in the same position at each assessment for at least 5 minutes before and during the assessment. Physical examinations at Weeks 7 and 14 in Phase 1 and Week 13 in Phase 2 are limited to vital signs and symptoms.

11.2 Clinical Laboratory Tests

Patients will have blood samples collected for routine clinical laboratory testing. The clinical laboratory parameters will be analyzed at the site's local laboratory. Laboratory assessments to be completed will include hematology, chemistry, and urine or serum pregnancy test (females of childbearing potential).

Laboratory assessments will be defined as follows:

- **Chemistry:** To include sodium, calcium, total protein, albumin, creatinine, blood urea nitrogen, total bilirubin, alkaline phosphatase, AST, ALT, potassium, chloride, bicarbonate, lactate dehydrogenase, and glucose.
- **Hematology**: To include white blood cell (WBC) with differential, platelet count, hemoglobin, and red blood cell (RBC) count.
- **Urine or serum preganancy test** – See section 11.7 below for further details.

Additional laboratory assessments may be conducted throughout the study as medically necessary.

11.3 Urinalysis

Patients will have urine samples collected for routine urinalysis. The urinalysis will include color, appearance, and dipstick for specific gravity, protein, white blood cell-esterase, glucose, ketones, urobilinogen, nitrite, WBC, RBC, and pH. Microscopic analysis of urine will be performed if indicated based on macroscopic examination and urine dipstick results.

11.4 ECG

The following parameters from 12-lead electrocardiograms (ECG) will be evaluated: heart rate, PR interval, QRS duration, QT interval, and QTcF interval.

11.5 Autoimmune Monitoring

Autoimmune monitoring will occur through laboratory measurements of ANA, TSH, erythrocyte sedimentation rate (ESR), and C-reactive protein. Other tests, such as rheumatoid factor (RF), T3, T4, and thyroid antibodies may be performed as clinically indicated. Furthermore, periodic physical examinations, including eye exam for dry eyes, lymph node and joint assessment, and skin exam for vitiligo and rashes, will be performed.

11.6 Injection Site Reactions

The grading scale for injection site reactions (ISRs) used in this trial can be found in Appendix 3. Grade 1 ISRs consisting of mild redness, erythema, and swelling around the injection site are anticipated. Grade 1 reactions should dissipate over several days to a week with no special treatment. All ISRs should be recorded on the Injection Site Reaction CRF page. Attempts to obtain photographs at the peak of severity and at follow-up visits which show resolution over time are encouraged. A ruler should be in the field of view to allow measurement of the size of the reaction. If the patient consents, the de-identified photograph(s) should be appended to the ECRF.

11.7 Pregnancy

All female patients of childbearing potential will have a urine or serum pregnancy test performed at Screening, Baseline, and End of Treatment.

Female patients who become pregnant during the study should discontinue study medication immediately. The patient will receive counseling from the investigator or designee regarding the nature of the study medication and the potential risk on fetal development.

11.7.1 Time Period for Collecting Pregnancy Information

The time period for collecting information on whether a pregnancy occurs is from the Screening visit to four weeks after the last dose of study medication. Information on pregnancies identified prior to study product administration does not need to be reported to Heat Biologics.

11.7.2 Action to Be Taken if Pregnancy Occurs

The investigator will notify Heat Biologics, or designee, within one week of learning of a patient's pregnancy. The patient will also be followed to determine the outcome of the pregnancy. Information on

the status of the mother and child will be forwarded to Heat Biologics, or designee. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE (see AE/SAE section of the protocol).

A spontaneous abortion is always considered to be an SAE and will be reported as such. Furthermore, any SAE occurring as a result of a post-study pregnancy and that is considered reasonably related to the investigational product by the investigator will be reported to Heat Biologics. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

11.7.3 Action to be Taken if Pregnancy Occurs in a Female Partner of a Male Study Subject

The investigator will attempt to collect pregnancy information on any female partner of a male study patient who becomes pregnant while participating in this study. The investigator will record pregnancy information on the appropriate form and submit it to Heat Biologics, or designee, within one week of learning of the partner's pregnancy. The partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to Heat Biologics, or designee. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

11.8 Adverse Events (AE) and Serious Adverse Events (SAE)

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE, as provided in this protocol. During the study when there is a safety evaluation, the investigator or site staff will be responsible for detecting, documenting, and reporting AEs and SAEs, as detailed in both this section of the protocol and in the AE/SAE section of the study procedures manual. AEs should only be recorded for up to four weeks following the last dose of study medication, unless the AE is considered related to the study medication, which requires that the AE be reported regardless of the amount of time that has passed since receiving the last dose of study medication.

11.8.1 Definition of an AE

An adverse event is any untoward medical occurrence associated with the use of a medicinal product in humans, whether or not considered related to the medicinal product (21 CFR 312.32 (a)). Note: an AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e., lack of efficacy), abuse, or misuse.

A suspected adverse reaction (SAR) is defined as any AE for which there is reasonable possibility that the drug caused the AE (21 CFR 312.32 (a)).

An AE or SAR is considered unexpected if it is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed or, if an Investigator's Brochure is not required or

available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application (21 CFR 312.32 (a)).

11.8.2 Definition of an SAE

The Code of Federal Regulations (CFR) Title 21 part 312.32 and ICH Guideline for Industry: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, ICH-E2a March 1995, as implemented by the US FDA, defines a SAE or serious adverse drug experience as any untoward medical occurrence at any dose that:

- Results in death (i.e., the AE actually causes or leads to death)
- Is life-threatening (with regards to determining if an AE is serious, "life-threatening" is defined as an AE for which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe. If either the investigator or the sponsor believes that an AE meets the definition of life-threatening, it will be considered life-threatening)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Results in a congenital anomaly/birth defect
- Results in any "other" important medical event. Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

11.8.3 Disease-Related Events or Outcomes Not Qualifying as SAEs

An event that is part of the natural course of the disease under study (i.e., disease progression) should not be reported as an SAE. Recurrence or progression of the patient's neoplasia will be recorded in the clinical assessments in the ECRF. Death due to disease progression is to be recorded on the Death ECRF page and not as a SAE. However, if the progression of the underlying disease is greater than what would normally be expected for the patient, or if the investigator considers that there was a causal relationship between treatment with vesigenurtacel-L or protocol design/procedures and the disease progression, then it must be reported as an SAE. Any new primary cancer must be reported as an SAE.

11.8.4 Clinical Laboratory Abnormalities and Other Abnormal Assessments as AEs and SAEs

Abnormal laboratory findings (e.g., clinical chemistry, hematology, and urinalysis) or other abnormal assessments (e.g., ECGs or vital signs) that are judged by the investigator as **clinically significant** will be recorded as AEs and SAEs if they meet the definition of an AE or SAE. Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as AEs or SAEs.

However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the investigator as more severe than expected for the patient's condition, or that are present or detected at the start of the study and do not worsen, will **not** be reported as AEs or SAEs.

The investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

11.8.5 Reporting Adverse Events

The investigator will record all directly observed AEs and all AEs spontaneously reported by the study patient on the *Adverse Event* ECRF. In addition, each study patient will be questioned about AEs.

Each AE should be described in detail on the *Adverse Event* ECRF and SAEs on a *Serious Adverse Event* form and include the following information: start and stop dates, CTCAE v. 4.03 grading, relationship to study medication, action taken, and outcome. AEs should be recorded from time of first dose up to four weeks following the last dose of study medication regardless of the causal relationship to the study medication. AEs considered related to study medication should be recorded at any time regardless of when they occurred.

The investigator will also assess the possible relationship between the AE and the study medication as well as any concomitant medications according to the following criteria:

- Related: AE and administration of study product are related in time, and a direct association can be demonstrated.
- Not related: AE is clearly explained by another cause not related to study product.

Event outcome will be recorded using the following categories:

- Recovered/resolved
- Not recovered/not resolved
- Recovered/resolved with sequelae
- Fatal
- Unknown

11.8.6 Prompt Reporting of SAEs

All SAEs, whether or not considered related to the investigational product, must be reported within 24 hours of becoming aware of the event to the Medical Monitor listed on the second page of this protocol. The Medical Monitor will require the following patient information as listed on the SAE form:

- Subject identification, including patient study number, initials, and sex
- Date of first dose of investigational product
- Total dose and number of doses administered
- Date and amount of last dose of investigational product

- Whether the patient was taking investigational product at the time of the AE
- Date, duration, and description of AE
- Events and/or symptoms leading up to the AE
- Action taken, including whether patient was withdrawn from study
- Concomitant therapy (including doses, routes, and regimens)
- Pertinent laboratory data
- Medical history (including time on study prior to AE and history that might be related to the AE)
- Dosing status of investigational product (e.g., interrupted, discontinued, dose changed)

In addition to the above information, the Medical Monitor will require the investigator's assessment of the following:

- Intensity of the AE
- Investigator's assessment of the relationship of the AE to study treatment
- Outcome of the AE

Any necessary follow-up must be submitted within a reasonable time thereafter. The sponsor will promptly report SAEs to the FDA and other applicable regulatory agencies in accordance with Title 21 of the Code of Federal Regulations (CFR), Part 312.32 (21 CFR 312.32) and local regulatory requirements. The investigator should also comply with any applicable requirements related to the reporting of SAEs to the IRB/IEC.

The investigator will provide an SAE follow-up report to the sponsor. In this report, the investigator is to assess and record the SAE in detail, including the date and time of onset, description, intensity, duration, outcome, etiology, relationship to study drug, and action taken. Any SAEs that continue at the patient's last study visit must be followed until the event resolves or follow-up is agreed to be adequate by the investigator, Medical Monitor, and sponsor.

The clinical site investigator and the Medical Monitor will review each SAE report and evaluate the relationship of the SAE to study treatment and to underlying disease. Based on the investigator's and sponsor's assessment of the SAE, a decision will be made concerning the need for further action. The primary consideration governing further action is whether new findings affect the safety of patients participating in the clinical study. If the discovery of a new SAE related to vesigenurtacel-L raises concern over the safety of continued administration of study drug to patients, the sponsor will take immediate steps to notify the FDA and all investigators participating in clinical studies of vesigenurtacel-L.

Further action that may be required includes the following:

- Modification of the protocol
- Discontinuation or suspension of the study

- Modification of the existing consent form and informing current study participants of new findings
- Addition of any newly identified vesigenurtacel-L-related AEs to the list of expected AEs

12.0 STATISTICAL CONSIDERATIONS

12.1 General Statistical Considerations

Phase 1:

Data from Phase 1 of the study will be presented descriptively. Standard descriptive statistics will include the sample size, mean and standard deviation (SD), median, minimum, and maximum values for continuous variables. For categorical variables, the frequency of patients will be provided along with the percentage based on the number of patients with available data. Summaries will be based on observed data (i.e., no missing data will be imputed).

Analysis of the secondary efficacy parameters will follow the same approach as outlined for Phase 2 below.

Phase 2:

In Phase 2, the primary endpoint (proportion of patients alive and disease free at one year) between the two experimental groups and the control will be compared using Fisher's exact test and presented as odds ratios (OR) with 95% confidence intervals (CI) relative to the control group. For the statistical comparisons on the primary endpoint between the two experimental and control groups, there will be no adjustment for multiplicity. ORs will be generated with a simple logistic regression model with one year disease-free survival as the dependent variable and group as the sole independent variable (low dose and high dose vesigenurtacel-L vs. control). If the analysis of the primary endpoint does not suggest any dose response effect between the two vaccine arms, an exploratory analysis will be conducted where the two vaccine arms will be pooled and compared to the control arm for the primary endpoint (proportion of patients alive and disease-free at one year). The outcome will be presented as OR with 95% CI relative to the control group.

Efficacy comparisons between the monotherapy arm and any of the randomized arms will remain exploratory. However, safety and point estimates with appropriate measures of variance (SD, 95% CI) for the efficacy parameters for the fourth arm will be estimated.

The binary secondary endpoints will be presented as OR with appropriate 95% CI.

DFS will also be evaluated as a time to event endpoint, defined as disease recurrence or progression or death from any cause. For time to event endpoints, which will also include OS, time to cystectomy, and burden of repeat TURBT, survival curves will be generated by the method of Kaplan-Meier and compared with the log-rank test. In an exploratory analysis, the weighted log rank test will also be used. The weighted log rank preserves the statistical power that is lost due to the lag time effect in efficacy with immunotherapeutic agents.

Exploratory clinical and laboratory endpoints will be summarized descriptively by time point of collection. Statistical testing and CI will be provided as an aid in reviewing the collected data. A log10 transformation may be used as appropriate in order to determine 95% CI based on a t-test for the log-concentrations, and the bounds will be transformed back to the original scale for presentation purposes. Homogeneity between

treatment groups will be assessed using Wilcoxon rank-sum tests for numeric variables and Fisher's exact test for categorical variables.

An unblinded Interim Analysis may be performed when all randomized patients have completed the disease assessment at Week 25. The primary goal of this analysis will be to allow selection of a dose and dosing regimen for future manufacturing efforts. At the time of this analysis all patients will have been enrolled, and the outcome of this analysis will not impact continuation of the trial to the primary endpoint. The treatment assignment of individual patients will not be unblinded to physicians or patients.

All of the analyses will be performed using SAS® Version 9.1 (or later). Further details of the exact analysis methods can be found in the study-specific Statistical Analysis Plan.

12.2 Analysis Populations

Study populations are defined as follows

Phase 1:

Safety Population: defined as all patients receiving at least one dose of vesigenurtacel-L

Phase 2:

Intent-to-Treat (ITT): defined as all patients randomized into the study and who will be classified according to their assigned treatment group, regardless of the actual treatment received.

Safety Population: defined as all randomized patients who receive at least one dose of treatment (BCG, HS-410, or any combination thereof)

Per-protocol population: defined as all patients in the ITT population who do not have any major protocol deviations (including being non-compliant to the study drug)

Other sub-populations of patients for secondary and exploratory analyses may be defined at the time of statistical analysis and will be identified in any reporting of results.

Patients will be randomized to Arms 1-3 centrally using a stratified block design according to risk of recurrence (strata: high vs. intermediate risk) and CIS (strata: yes vs. no). The intent for stratification is to ensure balance between groups with respect to these important prognostic factors. Given the limited sample size, a formal subgroup analysis based on the stratification variables will not be undertaken. Patients who will not receive BCG will be consecutively allocated (non-randomized) into Arm 4 consisting of vaccine monotherapy.

Due to delays in the batch release of certain doses of vaccine, the randomization schedule may be temporarily revised from a 1:1:1 randomization to a 1:1 randomization, with one arm being briefly suspended. During the period of revised randomization, each patient will maintain at least a 50% chance of receiving vaccine versus placebo. Randomization strata will remain unchanged. Upon batch release of the vaccine the randomization will return to the original 1:1:1 ratio. In order to maintain the study blinding, temporary closure of certain arms will not be disclosed outside of the DMC except as needed for Informed Consent documents.

12.3 Accountability, Demographics, and Baseline Characteristics

Accountability information will be summarized for each phase, including the number of enrolled patients, dosed patients, and patients who terminated at the first disease assessment, and the number of patients withdrawn by reason. Also, separately, the number of patients with recurrence events, dropping out, or continuing in the study will be summarized in order to show the percent of subjects without an event still being followed.

Descriptive information on demographics and baseline data including age, sex, weight, height, body mass index, physical examination, and medical history will be provided in a summary table. Summaries will be provided by treatment group and overall for the ITT and Per-Protocol population classifications.

12.4 Safety Analysis

Safety analysis will be performed for the Safety Population in each phase of the study.

12.4.1 Adverse Events

Treatment emergent adverse events (TEAEs) will be defined as events that occur on or after the first dose of study medication. The Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary will be used for the coding of AEs. TEAEs, serious or CTC Grade 3 or 4 TEAEs, and TEAEs related to therapy will be summarized overall and by system organ class and preferred term by treatment group. These will summarize the number of events and the number and percent of patients with a given event. A Fisher's exact test will be provided to evaluate if the number of patients with an event within a specific system organ class is homogeneous across the treatment groups. In addition, the number and percent of patients with TEAEs will be provided by maximum severity. A summary of all TEAEs by system organ class and preferred term occurring in at least 5% of subjects in either treatment group will be provided by quarter.

12.4.2 Laboratory Assessments

All laboratory-based data will be presented as listings of all values as well as abnormal results judged to be clinically significant, which will also be reported as AEs. Numeric summaries of all observed and change from baseline laboratory evaluations will be provided by visit and treatment group, including chemistry, hematology, and urinalysis results. No inferential comparisons are planned.

12.4.3 Vital Signs

Numeric summaries of all observed and change from baseline vital signs will be provided by time point and treatment group, including blood pressure, heart rate, and temperature. No inferential analyses are planned for vital signs.

12.4.4 ECGs and Physical Examination

Physical examination data and changes will be presented as listings. ECG results will be presented as listings and summarized by treatment group and visit based on incidence of clinically significant abnormalities. No inferential comparisons across treatment groups are planned.

12.4.5 Other Assessments

Other collected data not specifically mentioned, including physical examinations and protocol deviations, will be presented in subject listings.

12.4.6 Safety of Vesigenurtacel-L (Phase 1 and Arm 4 of Phase 2 Only)

Safety is defined as the number of adverse events (AE)/serious adverse events (SAE) in patients receiving vesigenurtacel-L.

12.4.7 Safety of the Combination of Vesigenurtacel-L and BCG (Arms 1, 2, and 3 of Phase 2 Only)

Safety is defined as the proportion of AE/SAE in patients receiving the combination of vesigenurtacel-L and BCG compared to the proportion of AE/SAE in patients receiving the combination of placebo and BCG.

12.5 Efficacy Analysis (Phase 2)

All efficacy analyses will be based on the ITT population unless otherwise specified.

12.5.1 Primary Efficacy Analysis

12.5.1.1 1-year Disease-Free Survival (1-yr DFS)

One-year disease-free survival will be defined as the proportion of patients who are free from recurrent disease, progressive disease, and alive one year after the date of randomization/treatment assignment (Arm 4).

For the primary efficacy evaluation, disease-free survival at one year between the experimental groups and the control will be presented as the absolute difference in proportions, as well as the OR, with the associated 95% CI.

12.5.2 Analysis of Secondary Efficacy Parameters

The Secondary Efficacy Parameters will be analyzed using Kaplan-Meier time-to-event methodology.

12.5.2.1 Time to Recurrence

Defined as the time from randomization to recurrence of disease to the same extent (stage and grade) as screening.

12.5.2.2 Time to Progression

Defined as the time from randomization to progression of disease to a greater stage.

12.5.2.3 Disease-Free Survival

Defined as time from randomization to recurrence or progression

12.5.2.4 Overall disease-free survival

Overall DFS is defined as the interval between the date of disease recurrence, progression, or death (whichever occurs first) and the date of randomization/treatment assignment (Arm 4) for patients without CIS. For patients with CIS at screening who have persistent disease at 6 months, the date of disease persistence will be defined as the date of randomization/treatment assignment (Arm 4) (i.e. DFS = zero).

Patients with CIS at screening who are disease-free by 6 months will have their overall DFS interval calculated between the date of disease recurrence, progression, or death (whichever occurs first) and the earliest date that the patient was determined to be disease-free. Patients will be censored at the last time of contact if recurrence, progression, or death has not been confirmed at the time of the analysis. Overall DFS will be analyzed using a log-rank test with a term for treatment assignment. In addition, Kaplan-Meier curves will be produced separately for each treatment group. The weighted log rank test will also be applied in an exploratory manner.

In a supporting analysis, a simple Cox proportional hazards model with treatment group as the sole independent variable will be built in order to estimate the hazard rate (HR) and 95%CI for overall DFS between the low and high dose vesigenurtacel-L groups relative to the control. A HR of less than one will provide initial evidence of a favorable outcome with vesigenurtacel-L. These analyses will be completed for the ITT and Per-Protocol populations.

12.5.2.5Overall survival

OS is defined as the interval between the date of death and the date of randomization/treatment assignment (Arm 4). Patients will be censored at the last time of contact if death has not been confirmed at the time of the analysis. OS will be analyzed using a log-rank test with a term for treatment assignment. In addition, Kaplan-Meier curves will be produced separately for each treatment group. The analysis will be completed for the ITT and Per-Protocol populations.

12.5.2.6Burden of Repeat TURBT

Defined as the proportion of patients with no repeat TURBT vs 1 TURBT vs 2 TURBT vs 3 TURBT etc within 12 months since randomization, within 18 months since randomization, and within 24 months since randomization.

12.5.2.7Time to Cystectomy

Defined as the time from randomization to cystectomy.

12.5.2.8Immune Response

Section 10.2.1 details how samples are run in duplicate or triplicate using ICS via flow cytometry or ELISPOT. The first step in the analysis of immunologic response will be to form the subject average across the duplicate or triplicate measurements recorded at each time point. In situations where only one measurement is obtained, the single value will be used in the analysis. If any values are in the range (0,1) inclusive, a value of 0.5 will be used in the analysis of count information on the log10 scale.

The observed and log10 transformed values will be summarized for each visit. In addition, the change from baseline will also be summarized descriptively. At each visit and for the last available visit, a sign-rank test will be used to evaluate the null hypothesis that the change from baseline is centered at zero separately for each of the dosing groups. Similarly, a Wilcoxon rank-sum test will be used to evaluate the null hypothesis that the observed and change from baseline values have a similar location ((i.e. median) between the low and high dose groups.) A 95% CI for the ratio of the differences geometric mean will be obtained by back-transforming the 95% non-parametric CI for the difference in log10 analysis. For the purposes of identifying the most important comparison, the analysis of the last assessment will be considered the primary analysis with other time points considered secondary analyses. Additionally, a repeated measures analysis will be completed modeling log10 transformed values as a function of visit, treatment, and a visit

by treatment interaction. Model results may not be reported if convergence is unattainable because of the small sample size.

These analyses will be completed using the ITT and Per-Protocol populations.

12.5.2.9Exploratory Efficacy Analyses

In an exploratory analysis, patients experiencing an immune response in all four treatment arms will be compared to those who did not experience an immune response. The analysis will include a univariate comparison of patient and clinical variables at baseline as well as a comparison of any difference between immune responders and non-responders for the following endpoints: proportion with progressive or recurrent disease at selected time points, disease-free survival, proportion undergoing post-treatment TURBT or fulguration or cystectomy, and overall survival.

In an additional exploratory analysis, the proportion of patients whose disease has recurred to a lower stage than at screening and the proportion of patients whose disease has recurred to the same extent as at screening will be compared between the experimental and control groups and presented as an OR with 95% CI.

12.6 Sample Size Estimations

12.6.1 Phase 1

Phase 1 is designed to provide some indication of safety and tolerability of the low dose of vesigenurtacel-L as a monotherapy. A sample size of 10 patients in the monotherapy setting is deemed suitable for an assessment of safety.

12.6.2 Phase 2

For the randomized portion, a sample size of 75 subjects in the ITT population was selected for this study.

The sample size assessment was based on the following assumptions:

- 75 patients will be randomized to yield 69 evaluable (25 patients per arm)
- A one year disease-free survival rate of 60% in the control and 90% in the respective experimental groups for an absolute difference of 30% in favor of the experimental treatments
- 10% drop-out rate
- Type I error (alpha) = 0.10 and using a one sided test with no adjustment for multiplicity
- Power = 80% to detect a 30% difference in one year disease-free survival between the vesigenurtacel-L groups and the control group
- Patients are followed for three years after the last patient is enrolled

13.0 STUDY CONDUCT CONSIDERATIONS

13.1 Regulatory and Ethical Considerations

Heat Biologics will obtain favorable opinion/approval to conduct the study from the appropriate regulatory agency in accordance with applicable country-specific regulatory requirements or local regulations where applicable prior to a site initiating the study in that country.

The study will be conducted in accordance with all applicable regulatory requirements, including a US IND. The study will also be conducted in accordance with GCP, all applicable patient privacy requirements, and the guiding principles of the Declaration of Helsinki. This includes, but is not limited to, the following:

- IRB/IEC/IBC review and favorable opinion/approval to conduct the study and of any subsequent relevant amending documents
- Patient informed consent
- Investigator reporting requirements

The sponsor will provide full details of the above either verbally, in writing, or both.

Written informed consent will be obtained for each patient before he or she can participate in the study.

13.2 Quality Control (Study Monitoring)

In accordance with applicable regulations, GCP, and Heat Biologics procedures, Heat Biologics monitors, or designee, will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and Heat Biologics requirements.

Heat Biologics will monitor the study consistent with the demands of the study and site activity to verify that the:

- Data are authentic, accurate and complete.
- Safety and rights of patients are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.
- The investigator agrees to allow the monitor direct access to all relevant documents.

13.3 Protocol Deviations

In general, a protocol deviation is an inadvertent excursion to, or non-compliance with, the IRB approved protocol. The investigator is responsible for ensuring the study is conducted in accordance with the procedures described in this protocol and should not implement any changes to the protocol unless it is required to eliminate an immediate hazard to the patient.

For the purposes of the protocol, deviations that fall into the following categories will be captured on the ECRFs. If the deviation affects the safety of the patient, the sponsor must be notified immediately. Other deviations outside of these categories will be reported to the IRB in accordance with local requirements, as applicable.

- Entered into the study without meeting eligibility criteria
- Developed withdrawal criteria during the study and was not withdrawn
- Received wrong treatment or incorrect dose
- Received excluded concomitant treatment
- Failed to collect data necessary to interpret primary endpoints

13.4 Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, Heat Biologics may conduct one or more quality assurance audits. Regulatory agencies may also conduct regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

13.5 Study and Site Closure

Upon completion or premature discontinuation of the study, the monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations, GCP, and Heat Biologics procedures.

In addition, Heat Biologics reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For this multicenter study, this can occur at one or more sites. If Heat Biologics determines such action is needed, Heat Biologics will discuss this with the investigator, including the reasons for taking such action, at that time. When feasible, Heat Biologics will provide advance notification to the investigator, where applicable, of the impending action prior to it taking effect.

Heat Biologics will promptly inform all other investigators, and/or institutions conducting the study if the study is suspended or prematurely discontinued for safety reasons. Heat Biologics will also promptly inform the regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action. If required by applicable regulations, the investigator must inform the IEC/IRB promptly and provide the reason for the suspension or premature discontinuation.

13.6 Records Retention

Following closure of the study, the investigator must maintain all site study records, except for those required by local regulations to be maintained by someone else, in a safe and secure location. The records must be maintained to allow easy and timely retrieval, when needed (e.g., audit or inspection), and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and staff. Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The investigator must assure that all reproductions are legible and are a true and accurate copy of the original and meet

accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back up of these reproductions and that an acceptable quality control process exists for making these reproductions.

Heat Biologics will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, or Heat Biologics standards/procedures; otherwise, the retention period will default to 15 years.

The investigator must notify Heat Biologics of any changes in the archival arrangements, including, but not limited to, the following: archival at an off-site facility, transfer of ownership of the records in the event the investigator leaves the site.

13.7 Provision of Study Results and Information to Investigators

When required by applicable regulations, the investigator signatory for the clinical study report will be determined at the time the report is written. When the clinical study report is completed, Heat Biologics will provide the investigator with a full summary of the study results. The investigator is encouraged to share the summary results with the patients, as appropriate. In addition the investigator will be given reasonable access to review the relevant statistical tables, figures, and reports and will be able to review the results for the entire study at the Heat Biologics site or other mutually agreeable location.

13.8 Data Management

The data collection tool for this study will be Heat Biologics-defined ECRF. Patient data necessary for analysis and reporting will be entered/transmitted into a validated database or data system. Clinical data management will be performed in accordance with applicable Heat Biologics standards and data cleaning procedures.

APPENDIX 1: BLADDER CANCER STAGING

Based on AJCC staging, which can be found at the following URL:
http://www.cancer.gov/cancertopics/pdq/treatment/bladder/HealthProfessional/page3

These T categories for bladder cancer refer to the primary tumor.

- **TX:** primary tumor cannot be assessed; information not known
- **TO:** no evidence of primary tumor
- **Ta:** noninvasive papillary carcinoma
- **Tis:** noninvasive flat carcinoma, also called flat carcinoma in situ. This means that the disease is still localized, or contained within the urothelium layer of the bladder wall. Cancer cells have not invaded the deeper layers of bladder wall tissue.
- **T1:** the tumor has grown from the layer of cells lining the bladder into the connective tissue below. It has not grown into the muscle layer of the bladder.
- **T2:** tumor has grown into the muscle layer
  - **T2a:** the tumor is in the inner half of the muscle layer
  - **T2b:** the tumor is in the outer half of the muscle layer
- **T3:** tumor has grown through the muscle layer and into the surrounding fatty tissue
  - **T3a:** this spread into the fatty tissue can only be seen with a microscope
  - **T3b:** this spread into the fatty tissue is large enough to be seen on imaging test or to be seen/felt by the surgeon
- **T4:** tumor has spread into nearby organs or structures. It may be growing in the stroma (main tissue) of the prostate, the seminal vesicles, uterus, vagina, pelvic wall, or abdominal wall

Histologic Features of Urothelial Papillary Lesions

	Papilloma	Papillary Neoplasm of Low Malignant Potential	Low-grade Papillary Carcinoma	High-grade Papillary Carcinoma
Architecture:				
Papillae	Delicate	Delicate. Occasional fused	Fused, branching, and delicate	Fused, branching and delicate
Organization of cells	Identical to Normal	Polarity identical to normal. Any thickness. Cohesive	Predominantly ordered, yet minimal crowding and minimal loss of polarity. Any thickness. Cohesive	Predominantly disordered with frequent loss of polarity. Any thickness. Often discohesive
Cytology:				
Nuclear size	Identical to Normal	May be uniformly enlarged	Enlarged with variation in size	Enlarged with variation in size
Nuclear shape	Identical to Normal	Elongated, round-oval, uniform	Round-oval. Slight variation in shape and contour.	Moderate-marked pleomorphism
Nuclear chromatin	Fine	Fine	Mild variation	Moderate-marked variation both within and between cells with hyperchromasia
Nucleoi	Absent	Absent to inconspicuous	Usually inconspicuous*	Multiple prominent nucleoli may be present
Mitoses	Absent	Rare, basal	Occasionally at any level	Usually frequent, at any level
Umbrella cells	Uniformly present	Present	Usually present	May be absent
*If present, small and regular and not accompanied by other features of high-grade carcinoma.				

Note: Only patients with high-risk disease (T1 and/or high grade and/or CIS) or intermediate-risk disease (Ta low grade with at least 3 of the following 4 risk factors: multiple tumors, tumor size >3cm, early recurrence (<1 year from previous TURBT), or frequent recurrences (>1 per year)) are eligible for participation in the trial.

APPENDIX 2: STAGES OF HEART FAILURE

The following stages of heart failure are based on the New York Heart Association (NYHA) functional classification system (taken from the Heart Failure Society of America http://www.abouthf.org/questions_stages.htm).

Class	Patient Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

APPENDIX 3: GRADING SCALE FOR INJECTION SITE REACTIONS

The grading scale is derived from the FDA Guidance for Industry (http://www.fda.gov/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/vaccines/ucm074775.htm#TOXICITYGRADINGSCALETABLES)

	Grade 1 **Mild**	**Grade 2** **Moderate**	**Grade 3** **Severe**	**Grade 4** **Potentially Life Threatening**
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	Emergency room visit or hospitalization
Erythema/Redness	2.5-5 cm	5.1-10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling*	2.5-5 cm and does not interfere with activity	5.1-10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis

* Induration/Swelling should be evaluated and graded using the functional scale as well as the actual measurement.

APPENDIX 4: PROTOCOL REVISION HISTORY

Protocol Change	Section Affected	Version where implemented
Change tumor volume collection from mg to ug (microns)	Section 10.1.5	Version 2.0, Amendment 1
Allow immune monitoring to be either by flow cytometry or ELISPOT to determine best methodology to advance into Phase 2	Synopsis and Section 10.1	Version 2.0, Amendment 1
Add ELISPOT assay details	Section 10.1.1	Version 2.0, Amendment 1
Remove the vial label from the protocol due to the potential for label changes over time	Appendix 4	Version 2.0, Amendment 1
Clarify in inclusion criteria that bladder risk assessment score must be ≥8 on the recurrence scale and ≤ 18 on the progression scale	Synopsis and Sections 4.1 and 6.2.1	Version 2.0, Amendment 1
Update timing of first dose relative to TURBT procedure to be consistent with the text elsewhere in the protocol	Schedule of Events (SOE)	Version 2.0, Amendment 1
Change DLT definition such that any AE >= Grade 3 that is possibly, probably, or definitely related to study drug be classified as such. (Formerly it was only "definitely" related items.) Also exceptions for systemic injections now ONLY include fever, myalgia, headache, or fatigue, nothing additional.	Section 5.2.1	Version 2.0, Amendment 1
Modify trial stopping rules such that enrollment is stopped and a full safety review is conducted if a death occurs within 24-hrs of vaccination if it is not clearly attributed to another cause. (Previously was only if it's definitely related).	Section 5.2.2	Version 2.0, Amendment 1
Modify statement that sites will be provided with optical discs as we will only do this upon request	Section 10.2	Version 2.0, Amendment 1
Outline definitions of Protocol Deviations that will be collected in the CRF and that need to be reported to the Sponsor	Section 12.75 and new section 13.3	Version 2.0, Amendment 1
Add section for definitions of ECG parameters as a listed procedure	Between former sections 11.3 and 11.4 - new section becomes Section 11.4	Version 2.0, Amendment 1
Fix formatting of bullet points around relatedness of AEs	Former section 11.7.5 - new numbering Section 11.8.5	Version 2.0, Amendment 1

Protocol Change	Section Affected	Version where implemented
Add "recovered / resolved" to AE event outcomes	Former section 11.7.5 - new numbering Section 11.8.5	Version 2.0, Amendment 1
Change definition of time to recurrence to be relative to the date of randomization rather than the date of dosing	Section 12.5.2	Version 2.0, Amendment 1
Remove immune response lab at Screening	SOE and Section 6.1	Version 2.0, Amendment 1
Remove requirement in footnote 1 of the SOA that requires screening labs to be done within 2 weeks of dose, since these labs will be redone at BL if the screening labs were taken more than 3 days prior to first dose	SOE	Version 2.0, Amendment 1
Update Week 7 and schedule of events window should be +/- 1	Section 6.2.3	Version 2.0, Amendment 1
Modify language from "pulse" to "heart rate" in the section on vital signs to be consistent with the rest of the protocol	Section 12.7.3	Version 2.0, Amendment 1
Combine "persistent disease" and "recurrent disease" and "progressive disease" into "evidence of disease" rather than separate categories since we can't tell them apart.	Synopsis, sections 3.1, 3.4, 6.2.3, 7.2.2, 12.2, 12.3, 12.6.3, SOE	Version 2.0, Amendment 1
Revise language in "dosing regimen" and "route" section to avoid duplication between the two and include clearer dosing for each cohort.	Synopsis	Version 2.0, Amendment 1
Add study schema to visually represent the overall design	Section 3.1	Version 2.0, Amendment 1
Add Sponsor protocol approval page	Front	Version 2.0, Amendment 1
Allow tumor curls or slides or fresh frozen tissue instead of FFPE and if necessary	Synopsis and Sections 6.2.1, 6.2.3, 6.2.7, 6.3, 10.1.5	Version 2.0, Amendment 1
Clarify that proteomics and recurrence rate comparison to placebo will only be done in the Phase 2 portion	Synopsis and Section 2.2	Version 2.0, Amendment 1
Clarify number of patients that will be enrolled	Synopsis and Section 3.4	Version 2.0, Amendment 1
Clarify that patients who discontinue vaccine at Week 7 due to evidence of disease will continue in long-term follow-up	Section 6.2.3 and SOE	Version 2.0, Amendment 1

Protocol Change	Section Affected	Version where implemented
Switch ordering of Appendix 2 and 3 and update references to each	Synopsis, section 4.1, Appendix 2 and 3	Version 2.0, Amendment 1
Correct "possible" to "possibly" in section defining dose limiting toxicities	Section 5.2.1	Version 3.0, Amendment 2
Add DLT escalation rules (eg if 1 of 9 patients get DLT we'll escalate, if 2/9 do, we'll stop).	Section 5.2.1	Version 3.0, Amendment 2
Remove reference on bottom of page 30 to additional backup sample for immune response timepoint (lingering error from previous version of protocol)	Section 6.1	Version 3.0, Amendment 2
Clarify that eye exam involves evaluation for dry eyes	Section 11.5	Version 3.0, Amendment 2
Remove risk assessment tool	Synopsis, Section 4.1, Section 6.2.1, SOE, Appendix 3,	Version 3.0, Amendment 2
Remove requirement that all injections occur with same needle.	Section 8.3.1	Version 3.0, Amendment 2
Rearrange synopsis content for clarity	Synopsis	Version 3.0, Amendment 2
Update product description to allow for revised formulation to be implemented without additional protocol amendment	Synopsis, Section 8.1	Version 3.0, Amendment 2
Clarify language in dosing administration around injection site rotation	Synopsis, Section 8.3.1	Version 3.0, Amendment 2
Note that missed doses will not be made up	Section 8.3.1	Version 3.0, Amendment 2
Combine DEC and DSMB into a single entity	List of Abbreviations, Synopsis, Section 5.1.2	Version 3.0, Amendment 2
Switch to single blinding (physician-patient)	Synopsis, Sections 3.1, 5.3, 6.4	Version 3.0, Amendment 2
Clarify definition of primary endpoint in Phase 1 as an increase of 2-fold over baseline in IFN-secreting CD8+ T cells	Synopsis, Section 3.5.1	Version 3.0, Amendment 2
Switch primary endpoint in Phase 2 from Time to Recurrence to Disease Free Survival to eliminate death as a competing risk and to include disease progression as well as disease recurrence; remove PFS as a secondary endpoint since DFS replaces it	Synopsis, Sections 2.1, 2.2, 3.5.1, 3.5.2,	Version 3.0, Amendment 2
Replace blood sampling for proteomic analysis with blood banking for future analyses	Synopsis, Sections 2.2, 3.5.2, 6.2.1, 6.2.5, 6.2.9, SOE, 12.4.1, 12.4.2,	Version 3.0, Amendment 2

Protocol Change	Section Affected	Version where implemented
Delete section 12.4 due to duplicity with section 3.5	Sections 12.4, 12.4.1, 12.4.2	Version 3.0, Amendment 2
Clarify that an overage of patients has been included in the sample size and that patients will not be replaced	Sections 3.1, 3.4, 7.2.2, 12.2	Version 3.0, Amendment 2
Remove reference to temperature monitoring device due to detailed description in pharmacy manual	Section 8.4.3	Version 3.0, Amendment 2
Remove batch number from the label	Section 8.4.2	Version 3.0, Amendment 2
Revisions to the statistical sections (analysis populations, sample size justification) etc.	Synopsis, Sections 12.X	Version 3.0, Amendment 2
Revise the dose escalation process such that the DEC will convene after at least one patient has received 6 vaccine doses and at least three patients have received two doses.	Synopsis, Sections 3.1, 5.1.1	Version 3.0, Amendment 2
Extend window of beginning of treatment from 8-10 weeks post-TURBT to 8-12 week post-TURBT.	Synopsis, SOE, Section 3.1	Version 3.0, Amendment 2
Change "enrollment" to "dosing" in description of dose escalation for clarity	Synopsis, Section 3.1, 5.2.2	Version 3.0, Amendment 2
Add detail in Appendix 2 to provide additional clarity about staging requirement	Appendix 2	Version 3.0, Amendment 2
Remove section 3.3 as duplicative to section 3.1	Section 3.3	Version 3.0, Amendment 2
Change regimen in Phase 1 and Phase 2	Synopsis, Section 3.1, Section 6.0, Section 8.5, Section 12.1	Version 4.0, Amendment 3
Define a BCG maintenance schedule	Synopsis, Section 3.1, Section 8.5.1, Section 8.5.2	Version 4.0, Amendment 3
Allow a single post-TURBT instillation of intravesical chemotherapy	Section 9.1	Version 4.0, Amendment 3
Analyze recurrence separately from progression	Section 10.1	Version 4.0, Amendment 3
Define persistent disease for patients with CIS	Section 10.1	Version 4.0, Amendment 3
Define the dose of BCG	Section 8.4, Section 8.5.2	Version 4.0, Amendment 3
Modify window between TURBT and start of treatment	Synopsis, Section 3.1, Section 6.2.1	Version 4.0, Amendment 3

Protocol Change	Section Affected	Version where implemented
Require 5 of 6 cycles of induction BCG	Section 8.4	Version 4.0, Amendment 3
Changed criteria for CrCl, albumin, and platelet laboratory parameters	Synopsis, Section 4.1	Version 4.0, Amendment 3
Adopt the standard definition of high-risk disease (T1 and/or high grade and/or CIS)	Synopsis, Section 4.1, Appendix 1	Version 4.0, Amendment 3
Exclude patients with prior prostatic pelvic radiation within the past 12 months	Synopsis, Section 4.2	Version 4.0, Amendment 3
Exclude patients with neo-adjuvant therapy prior to the most recent TURBT	Synopsis, Section 4.2	Version 4.0, Amendment 3
Exclude patients with allergy to peanuts	Synopsis, Section 4.2	Version 4.0, Amendment 3
Reduce time window for cardiac exclusion from previous 6 months to 3 months	Synopsis, Section 4.2, Appendix 2	Version 4.0, Amendment 3
Move directly to Phase 2 after cohort 1 in Phase 1	Synopsis, Section 3.1, Section 5.1, Section 6.2	Version 4.0, Amendment 3
Take immune response off the decision-tree and advance both doses into Phase 2	Synopsis, Section 3.1, Section 5.1, Section 6.2	Version 4.0, Amendment 3
Keep patients without progression or T1 high-grade disease on trial until 6 months even if evidence of disease	Synopsis, Section 3.1, Section 6.1, Section 6.2, Section 10.1	Version 4.0, Amendment 3
Add endpoints for recurrence at 6, 12, 18, and 24 months; DFS at 6, 18, and 24 months; overall DFS; repeat TURBT by 12 and 24 months; cystectomy by 12 and 24 months. Add 6-mo CR endpoint	Synopsis, Section 3.4.2, Section 12.5.2	Version 4.0, Amendment 3
Change primary endpoint in Phase 1 to safety and tolerability	Synopsis, Section 3.4.1	Version 4.0, Amendment 3
Change primary endpoint in Phase 2 to 1-yr DFS	Synopsis, Section 3.4.1, Section 12.5.1.1	Version 4.0, Amendment 3
Change title	Cover page, Sponsor Protocol Approval page, Investigator Protocol Agreement page, Synopsis	Version 4.0, Amendment 3
Clarify definition of recurrence events	Section 10.1	Version 4.0, Amendment 3
Allow a subset of intermediate risk patients	Synopsis, Section 4.1, Appendix 1	Version 4.0, Amendment 3
Add stratification factors for intermediate vs. high risk and presence of CIS	Synopsis, Section 8.5	Version 4.0, Amendment 3
Update introduction	Section 1.1, Section 1.2	Version 4.0, Amendment 3

Protocol Change	Section Affected	Version where implemented
Update Sponsor address and Medical Monitor	Contact Page	Version 4.0, Amendment 3
Change sample size	Synopsis, Section 3.3, Section 12.6	Version 4.0, Amendment 3
Fix typos, abbreviations, punctuation and spacing	Throughout	Version 4.0, Amendment 3
Add safety objective for Phase 2	Synopsis, 2.2 Secondary Objectives, 12.5.2 Analysis of Secondary Efficacy Parameters	Version 5.0, Amendment 4
Allow patients who have had fulguration or no surgery if they have CIS alone	Synopsis, 2.2 Secondary Objectives, 3.1 Study Design Overview, 4.1 Inclusion Criteria	Version 5.0, Amendment 4
Update Immune Response methodology, objectives, and endpoints	Synopsis, 2.2 Secondary Objectives, 3.4.2 Secondary Endpoints, 10.2 Immunolgic Response, 12.5.2.9 Immune Response	Version 5.0, Amendment 4
Remove blood sample for banking	6.2 Phase 2	Version 5.0, Amendment 4
Increase blood collected for Immunologic Response	6.2.1 Phase 2 Schedule of Events, 10.2 Immunologic Response	Version 5.0, Amendment 4
Remove specific dose information for BCG	Synopsis, 8.4 Dosage and Administration of BCG	Version 5.0, Amendment 4
Update sample size assessment assumptions (removed event and censoring times follow an exponential distribution)	12.6.2 Phase 2	Version 5.0, Amendment 4
Add fulguration at 12 and 24 months to secondary and exploratory objectives/endpoints	Synopsis, 2.2 Secondary Objectives, 3.4.2 Secondary Endpoints, 12.5.2.7 Proportion of patients undergoing post-treatment TURBT or fulguration by 12 and 24 months, 12.5.2.10 Exploratory Endpoints	Version 5.0, Amendment 4
Change most-recent TURBT procedure to baseline staging procedure	Throughout	Version 5.0, Amendment 4
Update creatinine clearance requirement	Synopsis, 4.1 Inclusion Criteria	Version 5.0, Amendment 4
Combine Removal of Patients from Treatment with Discontinuation from Study Treatment	Section 7.2.1	Version 5.0, Amendment 4
Indicate preference for tissue sections rather than FFPE	6.1 Phase 1, 6.2 Phase 2	Version 5.0, Amendment 4
Wrote out assessments for Weeks 37 and 49 in Phase 2	6.2.3.10 and 6.2.3.11	Version 5.0, Amendment 4

Protocol Change	Section Affected	Version where implemented
Update Figure 2	8.5.1 Schedule and Duration of Treatment	Version 5.0, Amendment 4
Remove frequency of liquid nitrogen replacement	8.6.3 Storage	Version 5.0, Amendment 4
Update CTCAE version to 4.03	11.0 Safety Assessments	Version 5.0, Amendment 4
Allow anti-allergics, antipyretics, and/or analgesics for local and/or systemic injection reactions	9.1 Permitted Medications and Non-Drug Therapies	Version 5.0, Amendment 4
Updated discontinuation language so that patients with evidence of disease may continue to receive treatment if in the patient's best interest at the investigator's discretion	Synopsis, 3.1 Study Design Overview, 6.1.1 Phase 1 Schedule of Events, 6.1.3.3 Phase 1 Assessments at Week 7, 6.1.3.7 Phase 1 Assessments at Week 21, 6.2.1 Phase 2 Schedule of Events, 6.2.3.5 Phase 2 Assessments at Week 13, 6.2.3.7 Phase 2 Assessments at Week 25, 6.2.3.10 Phase 2 Assessments at Week 37, 6.2.3.11 Phase 2 Assessments at Week 49, 7.2.1 Discontinuation from Study Treatment	Version 5.0, Amendment 4
Include exploratory analysis to pool both vaccine groups in Phase 2	Synopsis, 12.1 General Statistical Considerations, 12.5.1.1 1-year Disease-Free Survival	Version 5.0, Amendment 4
Increased non-heparinzed blood sample to 10mL	10.2 Immunologic Response	Version 5.0, Amendment 4
Removed magnesium laboratory	11.2 Clinical Laboratory Tests	Version 5.0, Amendment 4
Added analysis of urine immunology	Synopsis, 2.2 Secondary Objectives, 3.4.2 Secondary Endpoints, 6.2.1 Phase 2 Schedule of Events, 6.2.3.1 Phase 2 Baseline Assessments, 6.2.3.3 Phase 2 Assessments at Week 7, 6.2.3.5 Phase 2 Assessments at Week 13, 6.2.3.9 Phase 2 Assessments at Week 28, 6.2.3.13 Phase 2 Week 56, 10.2 Immunologic Response	Version 5.0, Amendment 4
Exclude patient with any condition requiring active steroid or other immunosuppressive therapy	Synopsis, 4.2 Exclusion Criteria	Version 5.0, Amendment 4
Exclude patients with prior treatment with a cancer vaccine	Synopsis, 4.2 Exclusion Criteria	Version 5.0 Amendment 4
Current serious cardiac arrhythmia no longer exclusionary	Synopsis, 4.2 Exclusion Criteria	Version 5.0, Amendment 4
Collect information on caffeine consumption	9.1 Permitted Medications and Non-Drug Therapies	Version 5.0, Amendment 4

Protocol Change	Section Affected	Version where implemented
Allow patients who had a radical prostatectomy with detectable PSA below the definition of biochemical recurrence per the Phoenix criteria and no radiologic evidence of metastatic disease or with PSA doubling time greater than one year and no evidence of metastases with no active therapy	Synopsis, 4.2 Exclusion Criteria	Version 5.0, Amendment 4
Added Heat Biologics logo	Cover page	Version 5.0, Amendment 4
Updated HS-410 to vesigenurtacel-L	Throughout	Version 5.0, Amendment 4
Updated vesigenurtacel-L or placebo to blinded study product	Throughout	Version 5.0, Amendment 4
Updated Grade 4 adverse event to probably or definitely related to study product	7.2.1 Discontinuation from Study Treatment	Version 5.0, Amendment 4
Added new section on discontinuation from study follow-up with text from 7.2.1	7.2.2 Discontinuation from Study Follow-Up	Version 5.0, Amendment 4
Added new section on discontinuation from study follow-up with text from 7.2.1	7.2.3 Lost to Follow-Up	Version 5.0, Amendment 4
Changed preparation of vesigenurtacel-L to manufacturing of vesigenurtacel-L	8.1 Description of Investigational Product, Vesigenurtacel-L	Version 5.0, Amendment 4
Indicated that site must contact IWRS for assignment of the dose vial at each dosing	8.3 Dosage and Administration of Vesigenurtacel-L and Placebo	Version 5.0, Amendment 4
Indicated that vesigenurtacel-L must be stored at ≤ -120°C	8.6.3 Storage	Version 5.0, Amendment 4
Clarify that no investigational agents allowed during treatment but no prohibited medications during follow-up	9.2 Prohibited Medications and Non-Drug Therapies	Version 5.0, Amendment 4
Added IBCG and AJCC	List of Abbreviations	Version 5.0, Amendment 4
Added ISR Grading Scale	New Appendix 3 and 11.6 Injection Site Reactions	Version 5.0, Amendment 4
Removed reference to Post-Study AEs and SAEs chapter in the study manual	11.7.2 Action to Be Taken if Pregnancy Occurs	Version 5.0, Amendment 4
Added definition of safety for Phase 1	12.4.6 Safety of Vesigenurtacel-L (Phase 1 Only)	Version 5.0, Amendment 4
Updated definition of safety for Phase 2 and moved from 12.5.2.1 to 12.4.7	12.4.7 Safety of the Combination of Vesigenurtacel-L and BCG (Phase 2 Only)	Version 5.0, Amendment 4

Protocol Change	Section Affected	Version where implemented
Stated that staging is based on AJCC	Appendix 1	Version 5.0, Amendment 4
Updated serum creatinine to ≤2.2 mg/dL or calculated creatinine clearance > 35 mL/minute per the Cockcroft-Gault formula	Synopsis, 4.1 Inclusion Criteria	Version 5.0, Amendment 4
Increased total sample size from 84 to 110, the number of patients in Phase 1 from 9 to 10, and the number of patients in Phase 2 from 75 to 100	Synopsis, 3.3 Number of Subjects, 6.4 Blinding and Minimization of Bias	Version 6.0 Amendment 5
Added a fourth treatment arm in Phase 2; patients who will not receive BCG will be enrolled in an open-label arm and receive 12 weeks of high dose vesigenurtacel-L followed by 3 courses of 3 once-weekly vaccine injections 3, 6, and 12 months after beginning vaccine therapy	Synopsis, 3.0 Trial Design, 5.3 Emergency Unblinding of Treatment Assignment, 6.0 Study Procedures, 8.5 Treatment Assignment	Version 6.0 Amendment 5
Updated the statistical analysis given the fourth treatment arm in Phase 2	Synopsis, 12.1 General Statistical Considerations, 12.2 Analysis Populations, 12.4.6 Safety of Vesigenurtacel-L, 12.4.7 Safety of the Combination of Vesigenurtacel-L and BCG, 12.5 Efficacy Analysis, 12.6 Sample Size Estimations	Version 6.0 Amendment 5
Cystoscopy/cytology and long-term follow-up will occur every 3 months for the first 2 years of follow up, then every 6 months for up to a year	Synopsis, 3.1 Study Design Overview, 6.1 Phase 1, 6.2 Phase 2 Schedule of Events, 6.3 Long-term Follow-up, 10.1 Evaluation of Disease	Version 6.0 Amendment 5
Updated the per protocol population definition	12.2 Analysis Populations	Version 6.0 Amendment 5
Updated the exclusion criteria on active malignancies in the past 12 months, added an exclusion for prior vaccination with BCG for tuberculosis, and added an exclusion for prior splenectomy	Synopsis, 4.2 Exclusion Criteria	Version 6.0 Amendment 5
Increased the number of trial centers from up to 17 to up to 20	Synopsis, 3.3 Number of Subjects	Version 6.0 Amendment 5
Added background information on BCG timing, the current BCG shortage, and immunotherapy in the setting of minimal residual disease	1.1 Bladder Cancer	Version 6.0 Amendment 5
Included possible synergy between inflammation from surgery and vesigenurtacel-L	1.2 Rationale for Vesigenurtacel-L Development	Version 6.0 Amendment 5

Protocol Change	Section Affected	Version where implemented
Updated Figures 1 and 2	3.1 Study Design Overview, 8.5.1 Schedule and Duration of Treatment	Version 6.0 Amendment 5
Allow patients with evidence of disease to continue on treatment longer than the next assessment if judged by the investigator to be in the patient's best interest	Synopsis, 3.0 Trial Design, 6.1 Phase 1, 6.2 Phase 2, 10.1 Evaluation of Disease	Version 6.0 Amendment 5
Replaced AE wording "possibly, probably or definitely related" with "related"	5.2.1 Dose Limiting Toxicities, 5.2.2 Trial Stopping Rules, 6.1.1 Phase 1 SOA, 6.2.1 Phase 2 SOA, 11.8 AE and SAE, 11.8.5 Reporting AE	Version 6.0 Amendment 5
Due to batch release delays of certain doses of vaccine, the randomization schedule has been revised.	Synopsis, 3.0 Trial Design, 5.1 Data Monitoring Committee, 6.4 Blinding and Minimization of Bias, 8.5 Treatment Assignment, 12.2 Analysis Populations, 12.6 Sample Size Estimations	Version 7.0 Amendment 6
Added abbreviation of DMSO	Synopsis, List of Abbreviations	Version 7.0 Amendment 6
No longer specify number of injections or dose per vial of product	Synopsis; 3.2 Justification of Study Product Administration; 6.1.1 Phase 1 Schedule of Events; 6.2.1 Phase 2 Schedule of Events; 8.1 Description of Investigational Product, Vesigenurtacel-L; 8.3 Dosage and Administration of Vesigenurtacel-L and Placebo	Version 7.0 Amendment 6
Removed excipient percentages for placebo	8.2 Description of Placebo	Version 7.0 Amendment 6
Removed references to UM-UC-3 cell line; added PC3 cell line	1.2 Rationale for Vesigenurtacel-L Development; 1.3 Description of Investigational Agent Vesigenurtacel-L	Version 8.0 Amendment 7
Revised Statistical Analysis methods to match Statistical Analysis Plan	12.0 Statistical Considerations	Version 8.0 Amendment 7
Removed direct reference to TCR sequencing vendor	10.2.4 TCR Sequencing	Version 8.0 Amendment 7

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